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U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

U.S. NATIONAL INSTITUTES OF HEALTH
ANNUAL REPORT OF INTERNATIONAL ACTIVITIES
FISCAL YEAR 1975

Prepared by

John E. Fogarty International Center

for

Advanced Study in the Health Sciences

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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PREFACE

This document is the seventh annual report of international activities published by the John E. Fogarty International Center for Advanced Study in the Health Sciences. It contains a comprehensive narrative review and analysis of the international activities undertaken by the National Institutes of Health in FY 1975. Two companion booklets, NIH International Awards for Biomedical Research and Research Training, FY 1975 and NIH Statistical Reference Book of International Activities, FY 1975, supplement this annual report.

Within this review, the many international activities of the National Institutes of Health and their contribution toward broadening the knowledge base of the biomedical sciences dedicated to the improved health of American citizens as well as those of other nations are discussed. A significant part of NIH international activities, including the participation of distinguished foreign scientists in the Scholars-in-Residence program and Fogarty International Center conferences and symposia, as well as bilateral cooperation, was undertaken under the auspices of the Fogarty International Center. Other activities providing international biomedical cooperation have been conducted under the administrative purview of several institutes and divisions of NIH. These organizations have contributed to the substantive content of this report with descriptive analyses of their activities, thereby providing a guide to the various types of NIH international programs.

One important aspect of international cooperation that is very difficult to quantify, and one that has not been included in this document, is the informal exchange and sharing of information between professional colleagues in the United States and overseas. This cooperation, of course, is as valuable to the fulfillment of NIH mission as those other, more formal international cooperative activities described herein.

This document was prepared by the International Cooperation and Geographic Studies Branch, Fogarty International Center, Dr. Joseph R. Quinn, Chief. This branch is responsible for the overall coordination within the Fogarty International Center of activities involving other governments.

Milo D. Leavitt, Jr., M.D.
Director
Fogarty International Center

INTRODUCTION

It has been the policy of the National Institutes of Health for many years to stimulate and support international biomedical research. Since the end of World War II, in particular, NIH also has sought to extend international biomedical cooperation, recognizing, of course, that the exchange of data among scientists of many nations is fundamental to scientific progress. Thus, substantial research grant awards have contributed to the developing of productive working relationships between NIH and foreign laboratories. Other support of various kinds has also been instrumental in bringing foreign scientific competence to American science. Ultimately, these efforts seek to broaden the knowledge base of the biomedical sciences devoted to improved health for citizens of the United States and those of other nations.

In pursuit of these research objectives NIH undertook numerous international activities during fiscal year 1975. In addition to the continuation of ongoing grant and training awards, NIH scientists attended many international biomedical conferences, sponsored international symposia and seminars of various scientific and associated biomedical problems, received distinguished foreign biomedical scientists, and published several books and papers advancing NIH research programs. The Fogarty International Center, as the point of coordination for the international activities of NIH, initiated or was involved in a substantial part of the international cooperation in the biomedical sciences delineated in this report.

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I

FOGARTY INTERNATIONAL CENTER

CONCEPT AND PROGRAMS

FOGARTY INTERNATIONAL CENTER: CONCEPT AND PROGRAMS

In a speech before the Third National Conference on World Health in September 1963, Representative John E. Fogarty introduced the concept of a center to represent "...the visible and tangible embodiment of the nation's devotion to the use of science for peaceful purposes and the good of mankind." He envisaged a study center that would "... encompass conference facilities, laboratory and study space, and the living quarters to permit the assembly for discussion, study, and research of the outstanding health scientists of the world." Representative Fogarty died on January 10, 1967, before the realization of this concept. After his death, however, then Congressman Melvin Laird proposed the establishment of such a center as a living memorial to Mr. Fogarty. The Congress and the President approved this proposal, and on July 1, 1968, the John E. Fogarty Center for Advanced Study in the Health Sciences was realized.

The close of FY 1975 records the completion of the seventh year of operations for the Fogarty International Center. During the course of these years several programs have emerged as the principal activities of the Center and from which the Center has derived much of its character in attempting to fulfill the concept of Representative Fogarty and the Honorable Melvin Laird.

Generally, the Center's programs were designed to promote advanced study in the biomedical and related sciences and to develop practical methods to utilize the knowledge thus gained to improve the health and well-being of our contemporary society. The Center's programs encourage interaction, study, cooperation, and collaboration within the international biomedical community and provide opportunities for study and discussion of significant research, public health, medical, and biomedically related social and economic issues.

Specifically, the projects that constitute the general programs delineated above and that have developed within the Center over the past 7 years constitute a substantial spectrum of research and administrative support activities. One such program involves studies on preventive medicine that ultimately seek to investigate 15 areas of preventive medicine, including diseases of fetal development, trauma, emergencies and emergency care, communicable diseases, gastropathy, and endocrine and metabolic diseases. Another highly relevant and successful project involves the compilation and analyses of biomedicine and health care in a number of selected countries, with special emphasis upon the Soviet Union and the People's Republic of China.

Several studies covering various aspects of biomedicine and health care in the Soviet Union and China have been published over the past 7 years and several others are planned or in progress.

Still another imaginative project undertaken by the Center is the Scholars-in-Residence program whereby distinguished scholars undertake a period of residence at the Center to engage in research, individual study, and group interaction designed to produce original contributions toward advancing biomedical knowledge and to facilitate the exchange of ideas among biomedical scholars. Also of considerable current and potential significance is the bilateral cooperation in biomedical research with 19 foreign countries in which the Center serves to coordinate efforts for the United States Government. Although this cooperation is governed in most instances by agreements between the United States and other governments, there have been times when this cooperation has been attained through more informal bilateral arrangements. Thus far, this cooperation has yielded knowledge of foreign biomedical research and health care, as well as direct contributions to the advancement of American biomedical knowledge by foreign scientists.

In addition to these programs and projects briefly described above, the Center has engaged in several administrative programs designed to advance biomedical and related scientific knowledge in the United States:

1. Special Foreign Currency program (Public Law 480), which enables NIH to support biomedical research in "excess currency" countries abroad;

2. International Visitors Center, which serves as a focal point for the reception of foreign scientists;

3. International Research Exchange program, which has provided numerous opportunities for highly qualified foreign biomedical scientists to engage in advanced research in leading research institutions in the United States; and

4. International Education program, under which arrangements are made in the United States for biomedical training for foreign nationals receiving WHO and UN fellowships in the health sciences.

Finally, during our short past, the Center has provided a general coordinating function for all NIH international activities. In this role, the Center has reviewed foreign grants and contracts, published biomedical data from scientific observers abroad, and disseminated information to NIH obtained from participants in international scientific

conferences and symposia.

In summary, then, the Fogarty International Center for Advanced Study in the Health Sciences is attempting:

1. To promote advanced study in the health sciences through various mechanisms, such as conferences and seminars, support of scholars in residence on NIH campus, publications, and bilateral and multilateral cooperation;

2. To identify the legal, ethical, social, and economic problems that may arise from continuing biomedical research and to advance our understanding and insight into these problems; and

3. To stimulate research concepts in specific fields through interaction among the international and domestic biomedical research community.

There follows a description, in some detail, of the previously referenced FIC program and project operations during FY 1975 through which the Fogarty International Center staff sought to fulfill the several objectives set forth above.

Conference and Seminar Program

As part of the advanced study concept, the Conference and Seminar program sponsors interaction and collaboration among members of the international biomedical community and provides opportunities for study and discussion of significant biomedical, public health, and related social and economic issues.

In practice, the Conference program is developed around current directions in medical, biological, and behavioral sciences. Many of the meetings are in direct support of the research activities of the NIH, and criteria for sponsoring of conferences include a broad interest within the scientific objectives in addition to information exchange, and international priority.

Conferences convened to date can be classified into several conceptual areas: preventive medicine and health care delivery, environmental health, medical education, international health research and education, ethical and social problems in biomedicine, and advanced topics in biomedical research.

Preventive Medicine and Health Care Delivery

Improvement in the health status of the American people depends in great measure on the design and application of programs that emphasize the preventive aspects of human disease problems. Although health authorities generally agree with this thesis, a more precise definition is needed of effective methods or programs of prevention, financial resources required to implement these programs, and priorities to be assigned to research in preventive methodology. The need to assemble expertise in this field to elucidate mechanisms whereby the full impact of preventive medicine can be brought to bear on the solving of America's major health problems has been emphasized by the Office of the Assistant Secretary, DHEW, in the Forward Plan for Health.

Three years ago the Fogarty International Center initiated a series of comprehensive studies in preventive medicine. These studies, oriented by disease category, are charged to review and evaluate the state of knowledge and research in the prevention and control of human disease; identify knowledge gaps and areas requiring further research, including analysis of financial resources, techniques, and manpower; and identify problems encountered in applying preventive medicine and suggest corrective actions.

The first planning session of the organizational committee identified 15 major disease categories for detailed review by individual subcommittees. Of the six subjects selected for initial consideration, studies of diseases of fetal development and the neonatal period, derangements of dental health, communicable diseases, diabetes, and obesity have been completed and published. Additional subcommittees have been activated to consider renal disease, nutritional derangements, arthritis, maternal and child health, trauma, screening and health maintenance, and economic impact of ill health.

In an effort to coordinate divergent activities in preventive medicine, the Fogarty International Center has also undertaken a cooperative program with the Association of Teachers of Preventive Medicine. Designed to develop resource material for departments of preventive medicine, this program has the following objectives: to create resource material for individual departments in administration, teaching, research, and service; define department goals and enhance collaborative activity among departments of preventive medicine and other departments of health science schools; promote cooperative activities

among departments of preventive medicine via national joint teaching, research, and service programs; and provide consultative services to other agencies. The Fogarty Center has also cooperated with the Milbank Memorial Fund in its study of higher education for public health.

Among the 10 subjects considered, all have been completed and published:

-- New Health Practitioners
-- Teaching of Chronic Illness and Aging
-- Chronic Childhood Illness - Assessment of Outcome
-- Behavioral Sciences
-- Preventive and Community Medicine in Primary Care
-- Consumer Participation in Health Care
-- Toward an Educated Health Consumer
-- International and Extramural Teaching and Research Resources in Preventive Medicine
-- Academic Relationships Between Preventive Medicine and Public Health
-- National Teaching Resources in Preventive Medicine

To further assist coordination of preventive medicine in the United States, the Fogarty Center sponsored a National Conference on Preventive Medicine in June 1975, in which over 200 specialists in preventive medicine and allied fields participated. During the preceding year, eight Task Forces developed position papers in the areas of: historical perspective of preventive medicine in the U.S.; theory and practice of prevention in environmental health, delivery of preventive care in personal health services, social determinants of human health, consumer health education, training of health professionals for prevention, economic impact of preventive medicine, and quality control and evaluation. These task force reports were reviewed by the conference participants and recommendations were made for their implementation and for subsequent planning. The conclusions of the Task Forces were incorporated into DHEW Forward Plan for Health 1976-80.

Environmental Health

Conferences on environmental health topics have been sponsored in collaboration with the National Institute of Environmental Health Sciences. These meetings were in response to increased awareness of the contribution of the environment to disease processes and in support of the U.S. delegation to the UN conference, "Man and the Environment." The topics-controversy regarding the precise effect of environmental pollutants, uncertainty about the mechanisms by which they produce their effects, or simply lack of information as to the extent of the problem-

explored the roles of metallic contaminants, mutagenic agents, and multiple environmental factors in producing disease and the contribution of environmental factors to respiratory disease. These workshops have been made available to the public by publication.

Medical Education

This conference series developed largely in response to student unrest in the 1960's. This unrest reflected the need to revise medical curricula, making education more responsive to community needs. As a result, departments of community or social medicine were established and family practice came to be recognized as a speciality. The conferences sponsored by the Fogarty Center considered the student pressure for curriculum reform internationally, the role of biomedical research in the education of physicians, and the relationships between health care and medical education in the medical school. These conferences have all been published.

International Health Research and Education

Biomedical research and medical education are inextricably linked and mutually dependent on one another for their continued advancement and vitality. Institutions of medical education serve several purposes, traditionally represented by the triad of education, research, and service. In addition to training those who will provide health care, medical schools strive to cultivate an atmosphere conducive to research and to train those who will pursue careers in research and teaching.

Central to the purposes is the belief that virtually all countries share common problems and goals in educating and training health care providers. Direction and leadership are necessary in order to achieve the highest possible standards of medical care. Differences in approach to that goal are more a reflection of differences of cultural, social, and economic characteristics than of purpose. It is reasonable to believe that sharing ideas and experiences can be mutually beneficial.

The general objectives of the program follow:

-- To serve as a focal point within the Fogarty International Center and the National Institutes of Health for matters relating to international medical education at both undergraduate and postgraduate levels;

-- To accumulate, classify, and maintain information about current and changing patterns of medical education in advanced and developing countries;

--To evaluate such information with respect to health care problems and needs of individual countries and within the framework of their socioeconomic, cultural, and political characteristics;

-- To compare systems of medical education with one another and with established or changed patterns of medical education in the United States;

-- To initiate, support or assist the development of individual or collaborative studies or programs pertinent to its mission.

Ethical and Social Problems in Biomedicine

The Center has sponsored conferences on various social and ethical problems arising from advances in biomedical research and the application of these advances to medical care. The Center is ideally suited to this role, since it represents a nonpartisan meeting ground for discussion of these controversial areas. Topics considered have included changing family structure and control of human reproduction; new technological abilities for early diagnosis of human genetic disease and detection of persons who may transmit genetic disease to their offspring; the prospects for treatment of patients with genetic disease, and the ethical issues involved in genetic counseling; and the health hazards involved in experimentation with oncogenic and infectious viruses.

Advanced Topics in Biomedical Research

Support of meetings in this category is in recognition of the important role of research in the understanding of disease processes and in the development of early detection and better treatment of illness. Many of these conferences have provided support for the research activities of the various NIH institutes.

In addition, Fogarty Scholars and U.S. and foreign academicians have participated in identifying key problems in basic and clinical research that should be explored by bringing together scientists in various fields. Conferences sponsored recently include:

-- Cell Surfaces and Malignancy

-- Chemistry and Biology of the Kallikrein-Kinen System

-- Modification of Host Immune Resistance in the Prevention and Treatment of Neoplasia
-- Structure and Function of Fluorescing Cells
-- Chemistry, Biology, and Political Aspects of Uses of the Atmosphere

Scholars-in-Residence Program

Crucial to the study center concept, this program facilitates the work of individual scholars and the exchange of ideas among scholars, distinguished science leaders, science administrators, and promising young scientists. Individuals accepting an invitation to participate in the program are known as "Fogarty Scholars" during their period in residence. Invitations are limited to persons of distinction who - in the judgment of the director of the Center, his staff, and advisors - have the educational and cultural background plus research experience to make significant contributions to advanced study in national boundaries.

Scholars and invited participants are not limited solely to experience in the biomedical disciplines; they may also consider studying philosophic, social, economic, or legal issues related to health science. While in residence each scholar participates in one or more of the following types of activity:

1. Individual study: The scholar may make an assessment of the state of the art or a prospective study in a specific field. This approach can be directed toward preparation of a book, monograph, or scientific report. Working primarily on an individual basis, the scholar is encouraged to participate in other NIH workshops, conferences, and seminars.

2. Group Interaction: The scholar might prefer to collaborate with other scholars and invited consultants in considering a common topic for the purpose of developing recommendations or suggestions for the advancement of biomedical knowledge.

3. Research: At the invitation of an institute, the scholar might choose to spend a portion of his time in the laboratory. As a Fogarty Scholar, however, he is encouraged to participate in FIC-sponsored workshops, conferences, and seminars when appropriate.

The sum of $210,867 was expended from Fogarty International Center FY 1975 funds for the Scholars-in-Residence program. The following 14 distinguished scientists were

Scholars-in-Residence during FY 1975:

Dr. Karl Beyer, Visiting Professor, Department of Pharmacology, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, Pennsylvania.

Dr. Daniel Bovet, Professor of Psychobiology, University of Rome, Rome, Italy.

Dr. Ronald V. Christie, Professor Emeritus, Office of the Dean, McGill University, Montreal, Quebec, Canada.

Dr. Hugh Davson, Honorary Research Fellow, Department of Physiology, University College London, London, England.

Dr. Olavi Eranko, Professor and Chairman, Department of Anatomy, University of Helsinki, Helsinki, Finland.

Dr. George E. Godber, (Former) Chief Medical Officer, Department of Health and Social Security, United Kingdom, London, England.

Dr. Ragnar Granit, Professor Emeritus, Nobel Institute for Physiology, Karolinska Institutet, Stockholm, Sweden.

Dr. Gordon G. Hammes, Professor and Chairman, Department of Chemistry, Cornell University, Ithaca, New York.

Dr. Abraham Horwitz, Director Emeritus, Pan American Sanitary Bureau, Washington, D.C.

Dr. Elvin A. Kabat, Professor, Department of Microbiology, College of Physicians and Surgeons, Columbia University, New York, New York.

Dr. Herman M. Kalckar, Visiting Professor, Biological Chemistry, Harvard University Medical School, Boston, Massachusetts.

Dr. Charles P. Leblond, Professor and Chairman, Department of Anatomy, McGill University, Montreal, Quebec, Canada.

Dr. Dirk W. Van Bekkum, Director, Radiobiological Institute, Institute for the Organization for Health Research, Rijwijk, The Netherlands.

Dr. Paul C. Zamecnik, Director, Colis P. Huntington Labs, Massachusetts General Hospital, Boston, Massachusetts.

International Visitors Center

This major program service of the Fogarty International Center receives scientists from all parts of the world. The Visitors Center is responsible for developing appointments for foreign scientists and dignitaries at NIH and coordinating them with their visits to other research centers.

During FY 1975, 195 of the 247 visitors were from 43 foreign countries and represented every part of the academic world. The U.S.S.R. sent 24, the largest number of visitors; followed by the People's Republic of China with 19, France with 17, the Federal Republic of Germany with 14, and Italy with 13. Among the distinguished visitors to NIH were Mr. Osman Dana, Minister of Health of Lebanon; Prof. Hubert Curien, Director, General Delegation for Scientific and Technical Research (DGRST), France; Dr. Philippe Laudat, Scientific Director of INSERM, France; Dr. A. P. Burger, Vice President of CSIR, Union of South Africa; and Mr. Emile Krieps, Minister of Health of Luxembourg. Principal areas of interest to the visitors were laboratory science, 54 visitors; administrators, 51; medical science, 20; and medical educators, 18.

In November 1974, an eight-member pharmacology delegation from the People's Republic of China visited NIH, followed in May 1975 by the visit of an eleven-member molecular biology delegation. Both delegations were sponsored by the National Academy of Sciences.

Another responsibility of the Visitors Center is administrative management of the NIH Visiting Program, in which international scientists participated during FY 1975. Services included assistance with housing and other living arrangements in the area, health insurance, income taxes, visas, local educational facilities for dependents, preparation and processing of appointment documents and educational counseling for participants and other scientists who are seeking career opportunities away from NIH. Analysis of the program follows under a separate heading.

The Visitors Center also assisted 184 guest workers from 42 nations at NIH during FY 1975 with many of the same services rendered to scientists in the Visiting Program.

International Research Exchange Program

In Section 307 of the Health Services Research, Health Statistics, and Medical Libraries Act of 1974, Congress authorized the Public Health Service to participate with other countries in cooperative endeavors in biomedical research to "establish and maintain fellowships in the United States and in participating foreign countries." Under this legislation the Fogarty International Center offers International Research Fellowships and Senior International Fellowships. These fellowships are offered in conjunction with the International Research Exchange program, which evolved from an extension to citizens of other countries (on September 16, 1957) of the regular NIH Postdoctoral Research Fellowship program. These fellowships were administered by the Division of Research Grants until the international portion was transferred to the Office of International Research at NIH in 1961. In 1968 the newly established Fogarty International Center assumed the administration of the International Research Fellowship Program.

One thousand five hundred twenty-four new fellowships, funded under the program from FY 1958 through FY 1975, have provided opportunities for carefully selected highly qualified foreign biomedical scientists to participate in research under the tutelage of leading American scientists. Each year applications from prospective fellows are reviewed competitively for scientific merit by a panel of experts convened at NIH. Applications are assigned priority scores by the reviewers, fellowships awarded according to this ranking, and the amount of funds appropriated for the program for that year.

International fellows have made significant contributions to the research programs of their preceptors in their host laboratories, thereby advancing the United States capability for diagnosis, treatment, or prevention of disease. The fellows bring different points of view to research problems and sometimes introduce new and innovative methodology developed abroad. Typically, they exhibit a high capacity for hard work and diligent devotion to research as reflected in their active participation in seminars and discussions and through their numerous publications in scientific literature. In FY 1975, 76 new International Research Fellowships and 26 second-year fellowships were awarded, at a total cost of $1,344,306.

In August 1974, with the establishment of the Senior International Fellowship program, the program of NIH-sponsored fellowships became a two-way exchange. The senior program enables carefully selected midcareer American

academic faculty members to work in the place of their choice abroad. The purpose of the program is to increase the interchange of ideas of mutual interest in basic or clinical research and academic studies. It is intended that the award will be a career-enhancing experience with mutual benefit to the fellow and his foreign host. Awards are made on the basis of scientific merit of the application and the competition is keen. During FY 1975, 28 Senior International Fellowships were selected for award from 45 applications. The funds expended for this program amounted to $444,227.

Another portion of the International Research Exchange program administered by the Fogarty International Center is the group of fellowships offered to young American postdoctoral scientists by the Swedish Medical Research Council and the Swiss National Science Foundation. Each year these two countries sponsor three fellowships each. The Fogarty International Center advertises this program annually, sends out application kits, and reviews applications for the two sponsoring countries. The review procedure is the same as for the International Research Fellowships; the applications with their assigned priority scores are forwarded to Sweden or Switzerland for final selection of the fellows by the sponsor. Since 1964 the Swedish Government has sponsored 28 American fellows; the Swiss have sponsored 9 since their program was established in 1973.

Visiting Program

Initiated in August 1950, this program sought the participation and assistance of outstanding young scientists for specialized research training as Visiting Fellows and for substantive contributions to the progress of NIH research as Visiting Associates and Visiting Scientists. Many centers of scientific research in the United States and abroad will benefit from the training and expertise acquired by these scientists in the NIH Visiting Program.

The growth pattern of the program has continued at a constantly accelerating rate. In FY 1965 there were 157 participants at a cost of $1.2 million; in FY 1970, 214 at $2.1 million; and FY 1974, 433 at $4.8 million. The following table contrasts the two most recent years:

	FY 1975	FY 1974
Visiting Fellows	302	231
Visiting Associates	121	106
Visiting Scientists	121	96
Total participants	544	433
Total countries	51	47
Total cost	$6.5 mil.	$4.8 mil.

In FY 1975, the following countries sent the most scientists in the Visiting Program: Japan 117, India 64, United Kingdom 43, Israel 38, Italy 31, and Taiwan 28. In addition, NCI had the largest number of Visiting Program participants with 133, followed by NIAMDD with 86.

Under this program, NIH bureaus, institutes, and divisions invite scientists of their choice to participate in one of the three program categories. In contrast to Visiting Associates and Scientists, whose award is for the performance of services for NIH, the Visiting Fellows' award supports postdoctoral research training. Awards are made to individuals with a doctoral degree in a health science field whose postdoctoral experience does not exceed 3 years. The sponsor of the Visiting Fellow is expected to provide educational opportunities similar to those provided by university faculty members to their postdoctoral fellows.

Special Foreign Currency Program

The National Institutes of Health (NIH) Special Foreign Currency Program, imprecisely referred to as the "PL 480 program," enables NIH to participate in collaborative research efforts of the international biomedical research community and to utilize resources of selected countries to further the attainment of the domestic goals of the institutes and of the host countries. This program brings the talents of U.S. scientists and those from other countries to bear on biomedical science and information exchange problems of mutual interest. It is funded with currencies, designated by the Department of the Treasury as excess to the immediate needs of the U.S. that have primarily accrued under Public Law 480 from the sale in past years of surplus agricultural products. Thus, it neither contributes to the flow of dollars abroad nor uses new tax revenues.

The collaborative character of the NIH program requires that there be a scientist from NIH (intramural) or a U.S. academic institution (extramural) as a participant. Research projects are selected by individual institutes on the basis of technical merit and potential contribution to institute research objectives. Projects are also subject to review within the host country for technical merit and conformance with its national priorities. The research activities are conducted under formal agreements entered into by NIH, as an agency of the United States, and the foreign government.

Funds for the Special Foreign Currency program are derived from the appropriation for "Scientific Activities Overseas," which for presentation purposes appeared in the NIH appropriation for several years and was transferred to the Office of the Assistant Secretary for Health (ASH) in FY 1975. The Office of International Health of ASH/DHEW has responsibility for formulating policy for administering the appropriation for the Special Foreign Currency program. Funds are allotted to NIH on the basis of conformance of projects to programs and priorities of DHEW and priorities of foreign countries negotiated by DHEW. The excess currency countries during this fiscal year were Burma, Egypt, Guinea, India, Pakistan, Poland, and Tunisia.

The U.S.-owned currencies in Israel and Yugoslavia have been reduced so that they are no longer "excess," and funds are no longer available in these countries for new projects or continuation of previously supported projects. This has severely curtailed the collaboration with the biomedical science communities afforded by this

program. In an effort to attenuate the severity of the financial impact and disruption of research programs and to formally recognize the need for maintaining collaboration, the Department of State has negotiated bilateral agreements with the governments of Israel and Yugoslavia through which remaining funds have been made available during a phaseout period to provide time in which to obtain replacement support. To avoid the disruption of the scientific community experienced in Israel and Yugoslavia, in the event of depletion of the U.S. balance of Polish currency, the long-standing agreement for health science cooperation with Poland has been amended recently. During this fiscal year bilateral agreements, which include a biomedical research component, have also been negotiated with Egypt and India. These bilateral agreements establish policies, procedures, and priority areas of mutual interest to which the NIH Special Foreign Currency program must conform. They will have a significant impact upon the development of the NIH SFC program and will become a major influence on its character. A more detailed review of the five agreements follows.

Israel

In FY 1968 it became apparent that balances of U.S.-owned Israeli pounds were depleted to the point where funds would no longer be available. The full impact of this depletion was realized by NIH in FY 1973, when the first projects reached the end of their previously committed period of support and could not be continued.

In anticipation of this, the Department of State and the Israeli government signed an agreement on September 27, 1973, establishing the U.S.-Israel Binational Science Foundation, to which each country contributed equal amounts of Israeli pounds in a total equivalent to $60 million. The income from the investment of these funds provides for some new activities as well as the continuation of projects and collaborations previously established under the Special Foreign Currency program. Approximately $2.1 million (equivalent) is available annually from this source to all U.S. Government agencies for the support of scientific and technological collaboration.

Either U.S. or Israeli scientists may apply for support, provided their requests represent collaborative research efforts. Applications are submitted to the Executive Director of the foundation in Jerusalem. The foundation arranges for technical merit evaluation of all applications, sending them to both U.S. and Israeli scientists by mail. From the projects that have passed this review, the Board of Governors of the foundation makes the final selection for funding. The foundation operates

independently of NIH, with the exception that NIH is requested to review projects to be funded for relevance to NIH biomedical research programs.

Yugoslavia

In March 1972 an accounting revealed that the U.S.-owned dinar holdings in Yugoslavia had been obligated by the science and technology agencies to such an extent that the currencies would no longer be in excess and that a maximum of $7.2 million (equivalent) was available for FY 1973 and FY 1974.

The Department of State negotiated the "agreement between the Government of the United States of America and the Government of the Socialist Federal Republic of Yugoslavia on scientific and technological cooperation," which was signed on May 18, 1973, by the Director, Bureau of International Scientific and Technological Affairs, Department of State, on behalf of the United States, and Mr. Krsto Bulajic, Director General, Federal Administration for International Scientific, Education, Cultural, and Technical Cooperation, on behalf of Yugoslavia. This agreement established a joint fund for the support of scientific and technological projects, including health, and a U.S.-Yugoslav joint board on scientific and technological cooperation to administer the fund in the amount of $14.4 million (equivalent) from equal dinar contributions by each country. At a meeting of the joint board May 14-18, 1973, it was apparent that the income from this fund would have little effect in moderating loss of financial support; the decision was then made to commit all the funds to provide limited support for projects during a phaseout period of 3 years. NIH was allotted funds for 24 projects. All active NIH projects in Yugoslavia are now operating with financial support from the joint fund.

The U.S.-Yugoslavia bilateral agreement has a unique provision for matching U.S. dollar support of any former NIH/SFCP or new research project of mutual interest on an equal-share matching basis through the joint fund administered by the U.S.-Yugoslavia joint board on scientific and technological cooperation.

Poland

A memorandum of understanding between the United States and Poland, signed March 14, 1962, designated NIH as the focus for development of a collaborative research program in the biomedical sciences. NIH served in this role until FY 1965 when in an effort to expand the scope of the program by involving other DHEW agencies, responsibility for administration and program development was transferred to the Office of International

Health, at that time in the Office of the Surgeon General of the Public Health Service and now in the Office of the Assistant Secretary for Health.

On March 15, 1973, during the visit of the Minister of Health of Poland, a revised memorandum of understanding was signed by the Secretary of DHEW and Dr. Marian Sliwinski, the Polish Minister of Health. For the first time this agreement formally provided for the exchange of scientists and the development of mutually agreed-upon priorities and the annual review and revision of these priorities.

On October 8, 1974, during the visit of Mr. Edward Gierek, First Secretary of the Polish United Workers Party, the health agreement of 1973 was revised and raised to the status of a "country-to-country" agreement and signed by the Secretary of State and Mr. Mieczyslaw Jagielski, Deputy Prime Minister and Chairman of the Planning Commission of Poland. This agreement included two new provisions: establishment of a U.S.-Polish joint committee for health cooperation and funding of DHEW projects for the Marie-Sklodowska Curie Fund. This joint fund was established by the agreement "Funding of Cooperation in Science and Technology," which was also signed at that time by the Secretary of State and Minister Jagielski. This document, which also provided for the establishment of a U.S.-Polish joint board, was an implementation of the "science and technology cooperation agreement" signed in October 1972 during the visit to Poland of the President of the United States.

With the establishment of the joint board and the joint fund, the Polish government has agreed to match the sums that DHEW deposits for support of NIH and other DHEW agency research projects. The administrative procedures incidental to operation of the fund are under development. The joint board selected nine NIH projects in the amount of $1,113,000 (equivalent) for support from the joint fund. These concern the neurosciences and immunologic and metabolic processes.

The priorities were given a second annual review at a meeting of the joint board on U.S.-Polish medical cooperation; it was agreed that those in effect during the past year would be continued. It was also agreed that oncology, which had been removed from the original list at the time of the first annual review because of lack of activity, would be reinstated as the result of recent developments in this field. The current priorities are (1) occupational and environmental health, (2) rehabilitation, (3) neurologic and psychiatric diseases, (4) health problems related to food and drugs, (5) infectious diseases and the immune system, (6) planning, delivery, and evaluation of health services, especially those to mothers and children, and

(7) oncology.

Egypt

An agreement on "principles of relations and cooperation between Egypt and the United States" was signed by Muhammed Anwar el-Sadat, President of the Arab Republic of Egypt, and by the President of the United States on June 14, 1974. The agreement established joint working groups for Suez Canal reconstruction, trade and economic growth, agriculture, technology, research and development in science, and medical cooperation. The purpose of the medical cooperation group, as stated in the agreement, is "... to assist the Government of Egypt to develop and strengthen its medical research, treatment, and training facilities." The joint working group on medical cooperation held its first meeting in Cairo October 28-November 1, 1974, at which time priority areas for cooperation were identified: (1) strengthening of health services, (2) health manpower and medical education, (3) production of pharmaceutical, biological, and medicinal products, (4) environmental health, and (5) biomedical research. During this meeting the delegates also prepared a preliminary delineation of the scope of each of the above priorities for consideration and development in greater detail by subsequent panels of expert consultants.

At the second meeting of the joint working group, July 7-11, 1975, it was found that other subcommittees for the aforementioned areas had subsequently assumed responsibility for some aspects of the biomedical sciences. The decision was made to appoint U.S. and Egyptian representatives to give further consideration to the needs of biomedical research in Egypt and, as appropriate, to identify priorities to replace those developed previously.

India

An "agreement between the Government of the United States of America and the Government of the Republic of India to establish a joint commission on economic, commercial, scientific, technological, educational, and cultural cooperation" was signed on October 28, 1974, by Secretary of State Kissinger and Mr. Y. B. Chavan, Minister for External Affairs of the Republic of India. The agreement provided for establishing subcommissions for the fields of economic and commercial development, scientific and technological cooperation, and education and cultural cooperation. Health was included, with industry and agriculture, as a responsibility of the subcommission on science and technology. The first meeting of this subcommission was held in Washington, D.C., January 27-29, 1975, during which priority areas were agreed upon as the basis for the program of cooperation. During the development of these priorities by the

subcommission, a major objective of the Indian delegation, comprised of representatives of the Ministry of Health and the Indian Council of Medical Research, was to assure that collaborative research efforts be directed toward investigations of those aspects of problems of importance to India. A further objective was the identification of new or additional researchers and institutions with the capability of carrying on productive research programs. The priority areas agreed upon for collaboration in the biomedical and health sciences are (1) communicable and infectious diseases, with particular emphasis on prevention and control techniques for such diseases as tuberculosis, leprosy, malaria, filariasis, (2) reproductive biology and fertility control, (3) health delivery systems for efficient utilization of medical and paramedical manpower, (4) nutritional, metabolic, and degenerative diseases, (5) toxicologic research in naturally occurring toxins in foods, pesticides, and drug residues, (6) other such areas of biomedical and health science research as may be proposed and agreed upon as being of mutual interest and importance.

International Education Program

Applications for training 478 international health professionals from 77 countries were processed during FY 1975. Of these, 348 (73 percent) were for fellows from the World Health Organization and other affiliated agencies of the United Nations. Another 48 (10 percent) were for participants in the Department of State Cultural Exchange Program. The remaining 82 applications (17 percent) included recipients of stipends from private foundations and voluntary agencies (such as the Governmental Affairs Institute, the China Medical Board, the International Planned Parenthood Federation, the Eisenhower Exchange Fellowships, and the Institute of International Education), as well as those who were self-financed, sponsored by their governments, or referred by other federal agencies. See Tables 1 and 2 for the distribution of such training programs, shown by countries of origin (arranged according to WHO regions) and fields of training.

In arranging, supervising, and evaluating the U.S. training programs of international health professionals, the branch staff has developed an extensive reservoir of health training resources. Diligent efforts to expand these resources have always been made to offer the widest choices possible for combining individual potential and background with the special needs of each country. One is cognizant of the world's health problems by a glance at the types of training requested: family planning, care of the aging, water quality, solid waste disposal, drug abuse, venereal disease control, air pollution, health care delivery and

economics, nutrition, migratory labor.

The branch is especially appreciative of the cooperation extended by the various institutes not only in Bethesda but also in the field laboratories. The branch continued its assistance to other federal agencies in the field of health training.

The branch again provided assistance to the World Health Organization in its selection of candidates from the United States for short-term fellowships abroad. In the interest of improving and expanding this country's health services, these fellowships are made available to selected U.S. citizens engaged in operational or educational aspects of public health. Inquiries were received from 883 individuals, resulting in 92 applications. From these, 45 were chosen for fellowships by the selection committee. Table 3 outlines the fields of training and states of origin of those awarded fellowships.

Table 1

Countries Represented by International Health Professionals, Applications Processed During FY 1975

Country by WHO Region	Sponsors			
	WHO-UN	State	Other	Total
Region I: Americas				
Argentina	7		1	8
Brazil	17		1	18
British Honduras	1			1
Canada	1			1
Caribbean Islands	36			36
Chile	5		2	7
Colombia	3			3
Ecuador	2		1	3
El Salvador		1		1
French Guiana	1			1
Guyana	8			8
Honduras	1			1
Jamaica	2			2
Mexico	10			10
Uruguay	1			1
Venezuela	11		1	12
TOTAL	106	1	6	113
Region 2: Europe				
Algeria	1			1
Belgium	1	1		2
Czechoslovakia	3			3
Denmark	1	1		2
France	2	18		20
Germany (Fed. Rep.)	1		1	2
Hungary	2			2
Iceland			1	1
Ireland	2			2
Italy		10	6	16
Netherlands	2			2
Norway		2	1	3
Poland	16			16
Romania	4			4
Spain	2		2	4
Sweden		1	1	2
Switzerland	2			2
United Kingdom	5		1	6

Country by WHO Region	Sponsors			
	WHO-UN	State	Other	Total
Yugoslavia	1	1		2
TOTAL	45	34	13	92
Region 3: Africa				
Ghana	1		1	2
Kenya	2			2
Lesotho	1			1
Liberia			6	6
Mauritius			1	1
Nigeria	1			1
Seychelles	1			1
Sierra Leone		2		2
South Africa		1		1
Uganda	1			1
Zambia	1		1	2
TOTAL	8	3	9	20
Region 4: Eastern Mediterranean				
Afghanistan	3		4	7
Egypt	1			1
Ethiopia	4		1	5
Iran	6		1	7
Iraq	3			3
Israel	8	1	3	12
Jordan	1			1
Lebanon	3			3
Pakistan	5	1		6
Sudan	1		1	2
Tunisia	1			1
Yemen	2			2
Other		1		1
TOTAL	38	3	10	51
Region 5: Southeast Asia				
Bangladesh	3		2	5
Burma		3		3
Ceylon (Sri Lanka)	10			10
India	56	2		58
Indonesia	8		3	11
Nepal	2			2
Thailand	8		10	18
TOTAL	87	5	15	107

Country by WHO Region	Sponsors			
	WHO-UN	State	Other	Total
Region 6: Western Pacific				
Australia	4		2	6
Japan	1	1	16	18
Korea	10		2	12
Malaysia	7		1	8
New Zealand	3	1		4
Philippines	25		2	27
Singapore	9			9
Taiwan			4	4
Vietnam	2		2	4
Other	3			3
TOTAL	64	2	29	95
TOTAL ALL REGIONS	348	48	82	478

Table 2

Field of Training of International Health Professionals, Applications Processed During FY 1975

Field of Training	Sponsors WHO-UN	State	Other	Total
Basic medical sciences	23	2	4	29
Behavioral sciences	10	2	1	13
Clinical medical sciences	33	4	1	38
Dentistry	6	1	-	7
Environmental health and ecology	132	1	11	144
Nursing	14	2	7	23
Other biosciences	4	-	3	7
Other health-related professional fields				
Drug abuse	18	1	1	20
Epidemiology	26	-	2	28
Family planning	14	-	12	26
Health administration	10	5	10	25
Hospital administration	2	18	18	38
Pharmacy	2	1	-	3
Veterinary medicine	6	-	-	6
Mental health	1	-	-	1
Other	8	10	5	23
TOTAL	87	35	48	170
Paramedical technologies				
Clinical	2	-	2	4
Environmental	1	-	-	1
Public health	13	-	1	14
TOTAL	16	-	3	19
Physical sciences	-	-	-	-
Sanitary Engineering	7	-	-	7
Statistics	11	-	-	11
Other	5	1	4	10
GRAND TOTAL	348	48	82	478

Table 3

World Health Organization Fellowships
Awarded to U.S. Citizens, 1975

No. of Fellows	U.S. States of Origin	Field of Training	Duration (Months)	WHO Regions Visited* 1	2	3	4	5	6	Total No. of Visits
3	Mass., Md., Ga.	Dentistry	3 1/2		2				1	3
5	Texas, Ill., Calif., Ariz.	Medical & Health Training	10 1/2		3		1	2	1	7
9	Mass., Okla., Md., Calif., Utah, Ark., Ky., Pa., Fla.	Medical Care	21 1/2		7			1	2	10
2	Ky., Mass.	Nursing Education	3 1/2		1			1	1	3
11	Calif., Ala., N.C. Ark., N.Y., Ariz., Conn., D.C., Ky., Minn.	Public Health Administration	22	1	10	1				12
7	Ala., Wisc., Pa., Fla.	Laboratory Science	7	1	2			1	1	5
2	Wisc., Md.	Epidemiology	4 1/2		2					2
1	N.Y.	Medical Records	1		1					1
1	D.C.	Health Education	1 1/2		1					1
1	Fla.	Environmental Health	2	1						1
2	Ohio, Pa.	Hospital Administration	3		2					2
1	Mich.	Medical Social Work	3		1					1
45	21 states plus District of Columbia		83	3	32	1	1	5	6	48

*See Table 1 for countries by region number.

Gorgas Memorial Institute

This institute was founded in 1921 as a living memorial to Major General William Crawford Gorgas, whose efforts in environmental sanitation led directly to the successful construction of the Panama Canal and to the virtual eradication of yellow fever from the great urban centers of tropical America. With continuous direct support from Congress since 1929, the institute has operated the Gorgas Memorial Laboratory in Panama City, Republic of Panama. Support of the research and training activities of the Gorgas laboratories comes from the Congressional appropriation, philanthropic donations, and research grants awarded by various agencies of the U.S. Government, especially the Public Health Service and the Army. The laboratories are one of the few research centers located in a near tropical area that possesses modern facilities and a well-trained staff. Another factor promoting the laboratory activities is the fact that the Gorgas Institute is an international organization capable of entering into cooperative arrangements and studies with authorities and investigators in any of the countries of the Western hemisphere. Capitalizing on these characteristics the program of the Gorgas laboratories has been devoted to research investigations of human disease, training scientists in tropical medicine, disease surveillance, and collaboration in international health efforts.

From its inception, the laboratory has concentrated its efforts toward the investigation and control of a variety of infectious diseases of particular tropical significance. Economic and social evolution has resulted in changing disease patterns, which requires broadening the scope of research activities of this laboratory. Thus, in addition to studies of vectorborne disease, major emphasis must be placed on enteric infections, nutritional derangements, and other human health problems influenced by geographic, environmental, genetic, and social factors.

In 1970 the Fogarty International Center assumed responsibility for the congressional justification of institute programs and, subsequently, encouraged a new interest in scientific advisory activities relating to program review and development. In 1972 the institute acquired responsibility for the operation of the Middle America Research Unit (MARU) a former field laboratory of the National Institute for Allergy and Infectious Diseases located in Ancon, Canal Zone. During its 16-year history, MARU has gained wide international respect for its work on such diseases as hemorrhagic fever, equine encephalitis, and hepatitis of several Latin American countries. Although MARU operations are now financed by annual contracts with NIH, the Gorgas Memorial Institute has already effected a consolidation of all its virological work at MARU.

Bilateral Agreements for Cooperation in Biomedical Research

In FY 1969, efforts were initiated to expand cooperation with other governments, involving biomedical research. This new effort involved programs for collaboration within existing or newly negotiated bilateral general science agreements. While deliberately drafted to embrace a wide spectrum of scientific areas, these programs encourage cooperating governments to share the cost of research. Expenditures in the cooperating country would be paid for by that government and those in the United States by the American Government. Over the past several years these arrangements provided additional vehicles to utilize that reservoir of scientific and technical biomedical personnel abroad who have contributed to the advancement of the world's biomedical knowledge.

These bilateral agreements in science and technology generally developed from a mutual desire to cooperate. A visit to the country in question by a team of specialists representing science and technology usually initiated the negotiation of the agreement.

Since these arrangements are very general in nature, the Department of State usually designated one agency, such as the National Science Foundation, of the United States Government to act as overall "executive agency" in coordinating implementation of these accords. If a cooperative biomedical research project is developed by a participating agency such as NIH under such a general agreement, the project application is submitted to the United States executive agency and its foreign counterpart agency for approval.

To date, under the aegis of these governments, a number of biomedical cooperative projects have been proposed and several exchanges of information and personnel have taken place between U.S. and foreign biomedical laboratories. Although much informal collaboration continued on the scientist-to-scientist level in a large number of the countries with which United States scientists have contacts, formal cooperative activities in the biomedical and health sciences were limited to relatively few. The countries involved in these general cooperative agreements for FY 1975 were France, Italy, and Japan.

France

The U.S.-France Agreement for Scientific and Technological Cooperation is administered by the U.S. Department of State and the French Ministry of Foreign Affairs. Many U.S. executive agencies participate in the agreement. The National Institutes of Health collaborate with their counterpart agency, the Institut National de

la Sante et de la Recherche Medicale (INSERM) on seven research projects:

1. Biological, Immunological and Biomedical Studies of Viruses Associated with Leukemia and Solid Tumors

   U.S. Investigator: Dr. J. B. Moloney, NCI
   French Investigator: Prof. G. Mathe, Hopital Paul Broussee, Villejuif

2. Basic Reactions of Pulmonary Tissues to Inhaled Pollutants

   U.S. Investigator: Dr. Claude J. M. Lenfant, NHLI
   French Investigator: Prof. P. Sadoul, Unite de Recherches de Physiopathologie Respiratoire, Nancy

3. Cellular Micro-Irradiation, Experimental Ultra-structural

   U.S. Investigator: Dr. W. N. Jensen, George Washington University and Dr. G. Brecher, University of Calif., San Fran.
   French Investigator: Prof. M. Bessis, Institut de Pathologie Cellulaire, Bicetre, Paris

4. Hormones and Cancer

   U.S. Investigator: Dr. E. V. Jensen, Director, Ben May Lab. for Cancer Res., Chicago
   French Investigator: Prof. E. E. Beauiles, Hopital de Bicetre, Paris

5. Myeloma Proteins

   U.S. Investigator: Dr. Henry Metzger, NIAMDD
   French Investigator: Prof. M. Seligman, Hopital St. Louis, Paris

6. Perinatology and/or Pregnancy and Maternal Health

   U.S. Investigator: Dr. Norman Kretchmer, NICHD
   French Investigator: Prof. A. Minkowski, Cochin Maternity Hospital, Paris: P. Royer, Paris, and others

7. Thyroglobulin Synthesis

   U.S. Investigator: Drs. J. E. Rall, J. Robbins and J. Wiff, NIAMDD
   French Investigator: Prof. S. Lissitzky, Faculte de Medicine, Marseilles

Collaboration involves primarily exchanges of information. However, three scientists from each side on each project may spend up to 3 months in the other country's collaborating project laboratories.

In the fall of 1974, when President Giscard D'Estaing of France and President Ford met in Martinique, it was agreed that cooperation in biomedical research should be expanded. Subsequently, through a series of visits by administrators on both sides, it was agreed to expand cooperation, including the establishment of a strategy committee for expanded cooperation in cancer research beyond that already carried out under the agreement.

Following the visit to Washington in June of 1975 by Mme. Simone Veil, the French Minister of Health, there was an exchange of views between Secretary Weinberger and Mme. Veil expressing joint support for the expansion of U.S. and French cooperative activities in cancer research through the INSERM-NIH agreement and giving approval to the proposal for the creation of a Strategy Committee.

Italy

The United States-Italy Science Agreement, signed in 1967, is a general "umbrella" agreement for scientific cooperation within which specific biomedical projects have been incorporated since FY 1970. During FY 1975, as with previous years, several ongoing and new projects were recommended by the National Science Foundation to be included within the above "umbrella" agreement. These projects, the principal researchers, including those projects now incorporated within the "umbrella" agreement and those pending approval either by U.S. agencies or the Conseglio Nazional delle Recherche are listed below under the institute through which they derive support.

NCI

1. Immune Response of Mice Against Experimental Leukemia

   U.S. Investigator: Dr. Gustavo Cudkowicz, State University of N.Y.
   Italian Investigator: Dr. Enzo Bonmassar, University Of Naples

2. Characterization of the Viral Genome Products (RNA and Proteins) Expressed by Cells Transformed by Mammalian RNA Tumor Viruses

   U.S. Investigator: Dr. Maurice Green, St. Louis U.
   Italian Investigator: Dr. Giancarlo Vecchio, University of Naples

3. Antigenic and Chemical Characterization of Cells Transformed by Adenoviruses

   U.S. Investigator: Dr. Fred Rapp, Penn. State U.
   Italian Investigator: Dr. Sergio Pauluzzi, University of Peruzio

4. The Role of Cyclic Nucleotides, in the Regulation of Gene Expression and Protein Synthesis in Animal Cells

   U.S. Investigator: Dr. Ira Pastan, NIH
   Italian Investigator: Dr. Stelio Varrone, University of Naples

NHLI

1. Development of Physico-chemical Techniques of Biological Interest

   U.S. Investigator: Dr. R. L. Berger, NHLI
   Italian Investigator: Dr. L. Rossi-Bernardi, University of Milan

2. Basic Mechanisms Underlying Erythropoiesis

   U.S. Investigator: Dr. Albert S. Gordon, New York University
   Italian Investigator: Dr. Cesare Peschle, University of Naples

3. Relationship Between the Metabolism of Triglycerides and Myocardial Function

   U.S. Investigator: Dr. Marilyn E. Hess, University of Penn.
   Italian Investigator: Dr. Adalgisa Bizzi & Silvio Garattini

4. Bioengineering Analysis of Microvascular Function

   U.S. Investigator: Dr. Marcos Intaglietta, University of Calif., San Diego
   Italian Investigator: Dr. Rodolfo Monti, University of Naples

5. Hemoglobin and Myoglobin Kinetic Studies

   U.S. Investigator: Dr. J. Parkhurst, University of Nebraska
   Italian Investigator: Dr. Giuseppe Geraci, University of Rome

6. Chemistry, Morphology, and Biological Activity of the Pulmonary Surfactant System in the Fetus and Adult, Normal and Abnormal

   U.S. Investigator: Dr. Emile M. Scarpelli, Yeshiva University
   Italian Investigator: Dr. Ermelando Cosmi, University of Rome

7. Patterns in Respiratory Control in Human Shock

   U.S. Investigator: Dr. John H. Siegel, SONY
   Italian Investigator: Dr. G. C. Castiglioni, CNR

8. New Modifications for Mechanical Ventricular Assistance

   U.S. Investigator: Dr. David B. Skinner, Johns Hopkins University
   Italian Investigator: Dr. Sergio Stipa, University of Rome

NIAMDD

1. Biochemical and Genetic Studies on the Structure of Histidyl-tRNA Synthetase and Methylation of Histidine-tRNA

   U.S. Investigator: Dr. Bruce N. Ames, University of California, Berkeley
   Italian Investigator: Prof. Francesco Salvatori and Francesco de Lorenzo, University of Naples

2. Mechanisms of Glucose Transport and the Action of Insulin

   U.S. Investigator: Dr. Pedro Cuatrecasas, Johns Hopkins University
   Italian Investigator: Prof. Gennaro Illiano, University of Naples

3. Mechanism of Repression of Biosynthetic Pathways: the Histidine Operon

   U.S. Investigator: Dr. Robert F. Goldberger, NIH
   Italian Investigator: Dr. G. B. Bruni, University of Naples

4. Purification and Characterization of Human Glycosidases and Study of their Possible Structural Alterations in Sphinglipidoes

   U.S. Investigator: Dr. Y. C. Lee, Johns Hopkins U.
   Italian Investigator: Dr. G. Romeo, University of Naples

5. Metabolic Effects of Acid-Base Disorders

U.S. Investigator: Dr. Arnold S. Relman, University of Pennsylvania
Italian Investigator: Dr. A. Tizianello, University of Genoa

NINCDS

1. Central Control of Neuromuscular Apparatus and Motor Coordination

U.S. Investigator: Dr. Emilio Bizzi, MIT
Italian Investigator: Dr. Vincenzo Tagliasco, University of Genoa

Japan

During FY 1975 the U.S.-Japan Cooperative Science Program, established in 1960 to foster a closer collaboration between scientists of the two nations, included within its program nine biomedical research projects listed below:

1. The Development of Pharmacological Probes for Studying the Cating Mechanism of Nerve Excitation

U.S. Investigator: Toshio Narahashi, Duke University Medical Center
Japanese Investigator: Issei Seyama, Hiroshima University School of Medicine

2. Reversible Interactions of Molecular Oxygen with Cobalt Porphyrin Complexes and their Apohemoprotein Complexes

U.S. Investigator: Takashi Yonetani, University of Penn. and 3 others

Japanese Investigator: Takao Kwan, University of Tokyo and 4 others

3. Biomembrane Formation and Function in Tetrahymena

U.S. Investigator: Guy A. Thompson, University of Texas - Austin
Japanese Investigator: Yoshinori Nozawa, Gifu University School of Medicine

4. Central Mechanisms of Motor Control

U.S. Investigator: Dr. Hiroshi Asanuma, Rockefeller University
Japanese Investigator: Dr. H. Shimazu, University of Tokyo

5. Development and Total Synthesis of Physiologically Active Natural Products

   U.S. Investigator: Dr. Lester A. Mitscher, Ohio State University
   Japanese Investigator: Dr. Tetsuji Kametani, Tohoku University

6. Biochemical Studies on Biologically Active Complex Carbohydrates

   U.S. Investigator: Roger W. Jeanloz, Harvard University
   Japanese Investigator: Tamio Yamakawa, University of Tokyo

7. Effects of Perinatal Exposure to Endocrine and Oncogenic Factors

   U.S. Investigator: Howard A. Bern, University of Calif., Berkeley
   Japanese Investigator: Noboru Takasugi, Okayama University

8. Amplification of Eukaryote DNA Fragments

   U.S. Investigator: Bruce M. Alberts, Princeton University
   Japanese Investigator: Kenichi Matsubara, Kyushu University

9. The Optical Properties and Structure of Deoxyribonucleic Acid by Electric Dichroism Techniques

   U.S. Investigator: Elliot Charney, NIH
   Japanese Investigator: Kiwamu Yamaoka, Hiroshima University

Geographic Health Studies

As suggested by the bilateral programs, the scientists and science administrators of the National Institutes of Health are actively seeking to expand their knowledge of foreign health activities and programs to provide new insights for improving the health of the American people. Important elements of all health activities, of course, include biomedical research, medical education, health manpower and health services. An analysis of these foreign health-related activities and programs may provide the U.S. Government health administrators with new insights in solving some of the complex problems relating to the improvement of health in the United States.

Recognizing the cultural and other historical influence upon foreign medical systems, no single country or government may have the type of medical care or health system

which will provide completely adequate health assistance desired by our citizens. A study of the best feature of foreign health systems, however, ultimately may provide a better understanding of the perspective within which health exists in the United States. Such a perspective, however, must include an improved comprehension of the political, economic, social, and other cultural aspects of society itself.

The Fogarty International Center, the first advanced study center of its kind within the Federal Government, therefore, is attempting to make information on the health systems of other countries as widely available as possible to both the pluralistic influences in the public and private sectors affecting the decision making processes in the United States. This information is also freely available to the medical communities and governments of other countries and international organizations. The specific objectives of these studies are: 1) To advance U.S. knowledge of health practices in different geographic regions or individual countries of Europe, South America, Asia, Africa and Australia; 2) To publish selected documents covering all phases of medicine and health in these different regions; and 3) To improve cooperation between clinicians, health scientists, and health administrators in the United States and other geographic areas.

The scope of the project may be divided into the following areas. Biomedical research: 1) The overall philosophy and organization of biomedical research; 2) Research trends and priorities; 3) Objectives; 4) Resources available; 5) Relationship to medical care. Interface Between Research and Education and Training: 1) The education of both professional and para-professional health manpower in general; 2) The role of the medical school; 3) The effect of health care needs upon medical education; 4) The financing of medical education; 5) The influence of public and private organizations upon medical school curricula. Interface Between Research and The Delivery of Medical Care: 1) The organization of health care systems; 2) Respective roles of public and private sectors in improving health; 3) The economics of health; 4) Special services to population groups such as mothers and children; 5) Geriatrics; 6) Mental health.

During FY 1975 a number of publications were prepared within the aegis of the Center's Geographic Health Studies:

Soviet Personalities in Biomedicine

This comprehensive volume, compiled in accordance with an interagency agreement between the Fogarty International Center and the Library of Congress, is considered a most valuable tool in furtherance of contact between American and Soviet biomedical research scientists. Listed

are 6,155 Soviet personalities associated with medicine and health-related research, their date and place of birth, education, specialization, career positions, professional activities, honors and awards, publications and other significant data. The personalities identified are those considered most likely to be involved in exchanges in fields of interest to the United States under the terms of existing and future agreements.

Soviet Biomedical Institutions: A Directory

The companion volume to Soviet Personalities in Biomedicine (above), this also was assembled by the Library of Congress under the interagency agreement. Its purpose is to provide United States biomedical scientists with a guide to the organization, personnel, geographic distribution, subordination, and research activities of selected Soviet medical and biological institutions. Described are some 1,200 institutions, including research, education and service facilities, and learned societies. Among the research facilities listed are institutes, independent laboratories, and research and treatment centers. Health care facilities included are hospitals, polyclinics, and dispensaries. Educational organizations listed include medical training institutes, university faculties of medicine and the military medical academy. Medical societies on the All-Union level are also included. The directory's detailed descriptions of Soviet facilities are considered most important toward the exchange of information, personnel and delegations under the expanded Agreement for Cooperation of 1972 and future agreements of this type.

A Barefoot Doctor's Manual

Translated from the Chinese publication of like title issued in September 1970 by the Institute of Medicine of Hunan Province, this volume has been issued for limited circulation in the United States. Its focus is upon improvement of medical and health care facilities in rural Chinese villages, with its primary purpose integration of the following: prevention and treatment; disease and symptoms, with stress on disease; traditional Chinese and Western medicine; the native and foreign; mass production and quality improvement. By delineating these principles and addressing the actual conditions at the rural level, the manual is aimed at meeting the working needs of the sub-professional "barefoot doctors" serving the broad rural population. Publication of this translated manual is toward further investigation and a better understanding of Chinese medicine and methods.

Soviet Research in Pharmacology and Toxicology

It is believed vitally important that workers in the

fields of pharmacology and toxicology be kept informed upon drug studies being conducted in other countries, and this publication is deemed valuable toward this end. The author, Dr. William H. Fitzpatrick, having expert familiarity with Soviet literature, has included 675 references, and there is also a comprehensive index making the volume an excellent reference text. It should prove of special interest to those concerned with drug research and development, in addition to those with a more general interest in the subjects covered.

China Medicine As We Saw It

Recognized by reviewers as another step toward filling in the spaces of the Chinese medical puzzle, this anthology of personal reports by professionals is the first such volume by recent visitors to the People's Republic of China. Reported on in 15 chapters are Chinese innovations in health; public health; its organization and status; public health practices; prevalent diseases; and biomedical research. Covered is a variety of subjects including: traditional and modern medicine, limb reattachment, acupuncture, fracture management, family planning, food and nutrition, occupational health, and the special significance of nasopharyngeal cancer in China. The volume is illustrated, and has several tables and an index.

Chinese Herbal Medicine

The author of this work, Dr. C. P. Li, is a distinguished Chinese-born scientist, who also was responsible for Anticancer Agents Recently Developed in the People's Republic of China, published earlier by the Fogarty International Center. Documented in this new volume are the practices of the Chinese utilizing medicinal herbs, resulting from an intensive study carried out by Dr. Li with the approval of the People's Republic of China. Included is an illustrated pharmacognosy of 44 individual herbs discussed in the monograph. It is believed that this work will prove helpful in further scientific investigation and toward a fuller understanding of the subject.

A Bibliography of Chinese Sources on Medicine and Public Health in the People's Republic of China: 1960-1970

This volume was also compiled by the Library of Congress by means of an interagency agreement with the Fogarty International Center. No fewer than 15,000 entries cover articles in journals and newspapers, and monographs. These are categorized under several headings including: acupuncture and moxibustion; allergy; anesthesiology; cardiovascular diseases; dentistry and oral surgery; dermatology; endocrinology, metabolism and nutrition; gastroenterology; hematology; infectious diseases; neurology; obstetrics and

gynecology; and 20 others.

Chinese Personalities in Biomedicine

The information contained in this publication was also assembled by the Library of Congress under the inter-agency agreement, using the same public sources as used for the Bibliography of Chinese Sources on Medicine and Public Health in the People's Republic of China: 1960-1970 (above). These sources comprise medical and related journals published by the PRC. In addition to listing the names of those prominent in Chinese biomedicine, the volume also provides data on their education, appointments, specializations, publications, memberships, and much other pertinent information.

Acupuncture Anesthesia

This publication is a translation from the Chinese volume of the same title, produced in November 1972 by a Shanghai-based editorial and writing team at the request of the Ministry of Public Health of the People's Republic of China. Acupuncture anesthesia is a comparatively recent development that has found increasing use and success since the time of the Cultural Revolution. This English-language version has been produced for limited circulation to scholars having a general or specialized interest in this aspect of health care.

Acupuncture Anesthesia in the People's Republic of China, 1973

Acupuncture anesthesia and therapeutic acupuncture are subjects that since 1970 have piqued the interest of the American public and the American medical profession. This volume, written by Dr. James Y. P. Chen, a Chinese-educated scientist-clinician with a distinguished American background, is intended to provide Americans with an overview of acupuncture anesthesia. During a visit to the PRC in 1973, Dr. Chen had opportunities to observe 30 operations performed under acupuncture anesthesia and to discuss this and other aspects of health care with numerous Chinese scientists, physicians, and other health professionals. The publication covers many aspects, including a summary of experience with this modality in the West, the selection and preparation of patients, selection of acupuncture points, application techniques, and the intra-operative and post-operative management of the patient.

Respiratory Research in the People's Republic of China

The current state of knowledge of pulmonary medicine reflects the contributions of scientists and physicians

working in many countries. The flow of information from the People's Republic of China was interrupted for many years, but it is now evident that there is much to learn from Chinese pulmonary medicine. Many pulmonary diseases are related to local ecology, and it is well known that some aspects of physiologic function may differ among ethnic groups. It is therefore considered fortunate that Dr. Frederick F. Kao, eminent respiratory physiologist and Professor of Physiology at State University of New York undertook to study the contributions of Chinese research in the field of respiration, and as a result prepared this monograph reviewing the many facets of pulmonary research and medicine in the PRC.

Urban Emergency Medical Service of the City of Leningrad

Translated from the Russian work of M. A. Messel, this publication discusses in detail the development and work of emergency medical services in the USSR, with particular emphasis upon the system prevailing in Leningrad. Described are the operation of central and district stations, methods of recording the stations' activities, the work of the station physician, volume of medical aid rendered, and the physician's tactics and operational methods. Also dealt with are the prevention of accidents, and the role of the station as an evacuation unit. The comprehensive volume contains many illustrations and tables.

An Economic Analysis of the Cooperative Medical Services in the People's Republic of China

The economics of cooperative medicine in the PRC comprise the main theme of this monograph by Teh-wei Hu, Visiting Research Professor at the Fogarty International Center. Much light is thrown upon the manner in which, in 8 years, the PRC established medical services relevant to basic medical needs and an effective medical system. The promotion of herbal medicine and the utilization of "barefoot doctors" are described as cost minimization approaches with great effect upon the economics of such a medical system. The publication has relevance as a study of interest for American specialists in the field of public health and the provision of medical services.

The Center as a Coordinator for NIH International Activities

For a number of hears NIH has sought the collaboration and scientific productivity of foreign scientists in fulfilling its mission of improving the health of the people of the United States and in contributing to the base of scientific knowledge upon which American scientists depend. The continuing limitation on the worlds resources, of course, have accentuated the NIH intent to utilize outstanding research opportunities regardless of geographic

location. Several different mechanisms are used to maximize benefit from these international resources, including grants and contracts to foreign institutions, publication of biomedical data derived from reports from abroad, and information from NIH participants in international scientific conferences and symposia. Thus, in addition to its other programs discussed above, the Fogarty International Center performs a coordinating role in making available for use of the NIH scientific community biomedical data derived through the aforementioned and other mechanisms.

II

INTERNATIONAL COOPERATION IN THE HEALTH SCIENCES BY COMPONENTS OF NIH

In addition to the activities in the international health sciences coordinated by the Fogarty International Center, many other components of NIH participate in international programs, projects, and other activities designed to promote the biomedical sciences. These include cooperation with national and international organizations throughout the world. The following summaries of the more important aspects of these cooperative efforts afford some measure of insight into these activities.

Since the passage of the National Cancer Act in 1971, the international activities of the National Cancer Institute (NCI) have been directed toward the development of a more coordinated program of international cooperation in cancer research and clinical care of the cancer patient. The interrelationship that has been established between the NCI and international institutions and organizations certainly will be mutually beneficial to all concerned, particularly since programs of international cooperation provide opportunities to immeasurably broaden our understanding of cancer cause and cancer prevention. For instance, variations in incidence rates for different types of cancer throughout the world are indicative of the role of geographic, social, and other environmental factors in their development. Thus "pooling" international efforts against cancer could more rapidly result in the synthesis of a comprehensible whole from those unique international components that might otherwise continue in diverse directions for a much longer period of time and with unnecessary expenditure of economic resources. Perhaps the greatest benefit to NCI, the national cancer program, and, ultimately, the cancer patient, is the sharing of international cancer research resources, particularly the resource of scientific intellect and its product of meaningful information.

During FY 1975, the Office of International Affairs within the Office of the Director, NCI, continued its effort of implementing the programmatic goals set forth in the act of 1971, as amended in 1974. A major effort has been devoted to developing a cohesive method for utilizing the cancer expertise that exists outside of the United States. Emphasis has been placed on accumulating all available data on cancer problems, analyzing that data, and disseminating it throughout the world anticipatory of such information serving as a data base for developing a comprehensive international program of collaborative cancer research.

International Cancer Research Data Bank Program

Soon after the enactment of the National Cancer Act, NCI established an International Cancer Research Data Bank (ICRDB) Program. During its first 2 years of activity the information needs of the cancer research community were identified, existing information systems described, and a scientific information system designed. Ultimately, a detailed plan evolved for the operation of this program.

Subsequently, a series of contracts were awarded for its implementation. The contracts - the majority initiated in FY 1975 - include efforts for (1) the rapid screening of 1,000 biomedical journals and other literature sources for all articles related to cancer, (2) preparation of abstracts of the cancer-related articles, (3) conversion of abstracts to magnetic tape and related data-processing operations required to produce and improve the ICRDB Data Base, (4) collecting descriptions of currently active cancer research projects from scientists located in research centers around the world, and (5) technical support to provide many special services needed by the ICRDB program.

The more than 46,000 abstracts describing recent results of cancer-related research and current cancer research activities are made available with ease to scientists and clinicians through on-line computer terminals located at more than 400 academic and research centers throughout the United States and, increasingly, in other countries. Using any combination of words or terms in the title, text, or index field, scientists can retrieve abstracts dealing with a specific cancer topic. The entire text of the retrieved abstracts can be viewed at a computer terminal or printed and mailed to the scientists. The system, which uses the MEDLARS computer system of the National Library of Medicine (NLM), is funded by an interagency agreement between NCI and NLM.

Concurrent with literature screening and abstracting is the collection and processing of approximately 10,000 brief descriptions of existent cancer research projects, including short outlines of cancer therapy protocols. This task is performed in the Current Cancer Research Project Analysis Center (CCRESPAC) of the Smithsonian Science Information Exchange, one of the ICRDB program contractors. These abstracts are then made available for on-line searching through the CANCERLINE network. In addition, CCRESPAC will offer another information product by producing some 30 technical bulletins listing current research projects in specific narrow subject areas. The bulletins will be distributed to scientists working on the same specific topic in order to establish direct communication with these colleagues.

At present, the ICRDB program is implementing and operating four Cancer Information Dissemination and Analysis Centers (CIDACs). These receive inquiries from comprehensive cancer centers, academic institutions, private laboratories, individual researchers, clinicians, and scientists throughout the world for the latest information on a subject. CIDAC subject specialists query the CANCERLINE data base, review the output, select relevant abstracts, and forward the results of the search to the user. This output includes not only the published litera-

ture available in CANCERLINE but also all ongoing research projects in the data base.

CANCERLINE can be accessed on an "as-needed" basis to respond to requests by the phone, mail, or personal visit. Conversely, CIDACs will function as a viable organization to stress the active dissemination of cancer research information by automatically distributing a steady stream of abstracts in specific subject areas to scientists working in those areas as a part of a program for the Selective Dissemination of Information (SDI). Current abstracts dealing with very narrow cancer subject areas will be sent to researchers working in those areas on a regular basis. Technical bulletins, each containing abstracts covering several years of results in a specific cancer research area, will also be published and forwarded to users. The inquiries, as well as the current awareness SDI products and technical bulletins, will all be obtained by computer searches of the CANCERLINE data base.

Other current, active ICRDB projects include (1) an International Registry of Tumor Immunotherapy Protocols containing descriptions of over 200 clinical trials of new immunotherapeutic procedures for treating cancer; (2) an International Cancer Epidemiology Clearinghouse that is funded jointly by ICRDB, the International Agency for Research on Cancer (IARC) in France, and the German Cancer Research Center in Heidelberg; (3) a contract with the International Union against Cancer (UICC) for support of the Committee for International Collaborative Activities (CICA) that promotes cooperation between cancer centers around the world, serves as an international advisory group for the NCI, and is assisting in the development and dissemination of ICRDB program products and services throughout the world; (4) a project with UICC to collect data on cancer therapy protocols from countries outside the United States; (5) the preparation of a directory listing and describing more than 1,000 cancer research organizations in countries around the world; (6) support of development of an improved international classification of diseases (ICD-(0)) for coding clinical cancer data under the auspices of the World Health Organization; and (7) support of a new program to collect information about cancer research projects and results in Latin America.

COOPERATIVE RESEARCH

Cooperative cancer programs are in effect with a number of foreign nations either as bilateral agreements between governments or formal agreements between the National Cancer Institute and a scientific institute or society of a foreign country.

U.S.-U.S.S.R.

Established by the 23 May 1972 U.S.-U.S.S.R. Agreement for Cooperation in the Fields of Medical Science and Public Health, American-Soviet cooperation is beginning to show dividends in almost all of the six cancer problem areas agreed to for joint study.

1. Cancer Chemotherapy

During the Third Working Meeting of U.S.-U.S.S.R. chemotherapists, April 1975, the status of clinical and experimental studies on 49 American and 66 Soviet drugs exchanged to date was examined. The results were considered impressive, especially with the U.S. nitrosoureas, hexylmethylmelamine, and DTIC; the Soviet's ftorafur and asaley; adriamycin from Italy; and the antracycline antibiotics from both countries. U.S. use of asaley and ftorafur, for example, has revealed preliminary clinical efficacy of ftorafur against adenocarcinoma of the gastrointestinal tract. Because of its decreased side effects, ftorafur (an analog of 5-fluorouracil) may prove to be effective clinically as a single therapeutic agent or when used in combination with other anticancer agents. Asaley is also showing some clinical promise, in selected cancers.

Detailed analyses of these data will be the primary content of a monograph, The Development of Drugs for the Treatment of Cancer, being prepared jointly. This monograph and another, Cancer of the Lung, are in final review for publication.

Both sides are continuing patient accrual in joint studies of lung cancer utilizing surgery with or without CCNU as the modes of therapy, continuing studies of epidermoid carcinoma, and undertaking pilot studies jointly on the efficacy in small cell carcinoma of the drug combination adriamycin-DTIC-vincristine.

Agreement was reached to organize a joint conference on ovarian cancer to exchange generalized experiences of both countries. It was agreed, as well, that for experimental purposes one or two new, potential anticancer drugs would be exchanged per year. There will be, in addition, an active exchange of drugs of synthetic and natural origin.

2. Cancer Immunology

During the second working meeting of U.S.-U.S.S.R. immunotherapists, April 1975, the present status of collaborative trials indicated that an impressive number of patients have been entered into the trials. The

Soviet results, especially those combining chemotherapy and immunotherapy, show considerable promise in the clinical management of metastatic melanoma.

An important feature of this meeting was the agreement to hold a conference on "Fetal and Tumor Antigens" in the Soviet Union in 1975 to permit an intense exchange of research information. This conference also provides to many young Soviet scientists the opportunity for active participation, as well as exposure to the most recent advances being made by Americans working in the broad interdisciplinary field of fundamental and applied immunology.

3. Cancer Virology

In the third working meeting of the U.S.-U.S.S.R. cancer virologists, May 1975, discussion focused on the following results: (1) isolation of a group of "potentially" oncogenic viruses from human cell lines in continuous culture by both U.S. and U.S.S.R. scientists; (2) isolation of "candidate" oncogenic viruses of the herpes group and type C oncornaviruses from two species of nonhuman primate inoculated with materials from leukemic humans; and (3) isolation and study of a virus associated with leukemia in cattle. These and other findings were reported during a 2-day symposium entitled, "Viral Neoplasia in Animals and Man."

4. Mammalian Somatic Cell Genetics Related to Neoplasia

When this working group met for the second time in June 1974, in Moscow, a symposium was held- "Mammalian Somatic Cell Genetics Related to Neoplasia." Five American and 11 Soviet papers were presented. Abstracts of the papers have been published in Russian in the Soviet journal, Genetika. A summary of the symposium will be published in the Journal of the National Cancer Institute.

Although it was agreed then to continue the program of cooperation as constituted during the first meeting, the anticipated scientific momentum has not appeared yet.

5. Cancer Epidemiology

During the second working meeting convened in February 1975, two important agreements were reached as a result of the information exchanged: A monograph will be published jointly on the current state of cancer epidemiologic research in the United States and the Soviet Union, and a joint study will be undertaken of the epidemiology of cancer of the breast.

Acknowledging the invitation of the U.S.S.R.

coordinator, a delegation of American epidemiologists spent October 5-18, 1975, in the Soviet Union exchanging information with Soviet cancer epidemiologists and visiting Soviet institutes engaged in cancer and cancer-related epidemiologic research. The primary objective was the design and development of a protocol for conducting the joint project on the epidemiology of cancer of the breast.

6. Cancer Control and Cancer Centers

Resulting from the second working meeting in Leningrad in May 1975, there was agreement to pursue several areas jointly: (1) the most effective means of early detection of breast cancer; (2) objectives and methodology essential to the rehabilitation of patients with breast cancer; (3) efficacy of cancer therapy (end results) using breast cancer as the model; and (4) the role of U.S. cancer centers and Soviet oncologic institutes in cancer control activities and their organization for oncologic research, both fundamental and clinical. This working group is expected to work in consonance with the specialists in cancer epidemiology.

Interestingly, joint projects to study cancer of the breast are included in five of the six problem areas, genetics being excepted.

Scientist Exchange

Twenty-six Soviet cancer specialists visited the NCI and other cancer centers in the United States for a total of 23.30 man-months. Thirty-nine scientists from the United States spent 20.20 man-months in visits and exchanges in Soviet oncologic institutes.

NCI-Japan Society for the Promotion of Science

During the first year of the U.S.-Japan Cooperative Cancer Research Program ten joint planning meetings and scientific symposia were held in the areas of chemical carcinogenesis, cancer virology, cancer immunology, cancer therapy, analytic epidemiology, breast cancer, lung cancer, bladder cancer, high-LET radiation therapy, cytology, and metastasis.

Analytic Epidemiology

In July 1974 plans were made for Japanese epidemiologists to work as exchange scientists in leading American laboratories and for several of them to attend NCI-sponsored meetings on national cancer programs to obtain information on cancer epidemiology. In February 1975 discussions ensued concerning a mutual program in

approaching occupational data in respect to vaginal and bladder cancer and the exchange of information and comparison of data on the occurrence of childhood cancer in Japan and the incidence rates in the United States. In addition, special emphasis was placed on the desirability of developing a Japanese counterpart of the U.S. county maps for cancer mortality.

Lung Cancer

During visits to Japan, lung cancer specialists from the United States were able to discuss the general program on the treatment and control of lung cancer in Japan and the most recent modalities of cancer chemotherapy. They had an opportunity to visit research facilities and to assess the clinical resources available for cooperative programs in lung cancer. A planning meeting was held on lung cancer morphology staging in order to develop a unified system for the diagnosis and treatment of lung cancer.

Breast Cancer

In July 1974 NCI-sponsored meetings enabled a delegation of Japanese cancer specialists to observe the planning and current programs of the Breast Cancer Task Force, as well as to attend a scientific conference on estrogen receptors. In February 1975 five Japanese cancer specialists participated in the Breast Cancer Task Force meeting held in San Antonio, Texas. At a special meeting, the Japanese group identified four areas for possible cooperation: (1) early and/or minimal breast cancer; (2) standardization and comparison of end results; (3) comparative epidemiology; and (4) standardization of criteria for evaluation of therapy. The Japanese Breast Cancer Working Group has been reorganizing its program to correspond to the organization of the NCI Breast Cancer Task Force. Future plans were discussed for long-range cooperation in these areas.

Cancer Therapy

A 3-day joint symposium was held on "Comparative Study on Cytosine Arabinoside and Cyclocytidine" and a workshop on the phase I study was held in Tokyo, February 13-15, 1975. Five American scientists and 30 Japanese participated. Experimental and clinical studies indicate that the American drug, cytosine arabinoside (Ara-C), is more effective than cyclocytidine (Japanese) in acute myelocytic leukemia and less toxic. The use of combination chemotherapy and combined modalities as well as the possibilities of cooperative phase I studies of new drugs were discussed.

A cooperative study on gastrointestinal tumors is

planned for December 1975 in Japan. A symposium on the status of bleomycin and nitrosoureas in Japan and the United States and surgical adjuvant approaches will be proposed to be held in Hawaii, February 1976.

Bladder Cancer

The result of a planning meeting in Wisconsin, February 1975, was general agreement that the Joint U.S.-Japan workshop conference on "Experimental Models for Bladder Cancer" be held in December 1975 during which 15-20 scientists from each country discuss and plan cooperative research on experimental model systems. In the spring of 1976, a workshop on the "Biochemical Aspects of Bladder Cancer" is planned in Kyoto, Japan. Tentative plans for meetings on pathology and treatment of human bladder cancer etiology, epidemiology of bladder cancer, and bladder tumor-host response were made for 1976-1978.

Cytology

In February 1975 five American scientists visited several research institutions and hospitals in Tokyo, Osaka, Fukuoka, and Sapporo to observe ongoing research in cytology, to review the state of the art of automated cytology in Japan, and to explore areas for future collaborative research in cytology.

It was observed that the Japanese scientists, in cooperation with several electronics firms, are developing instruments for cytology automation using automatic staining processes and cytologic scanners. The instruments measure the nucleus size and shape, nuclear-cytoplasm ratio, and nuclear density of the specimens. The instrumental developments are similar to those in the United States. It was observed that more attention should be placed on the preparation and standardization of specimens for these studies.

Long-range objectives for cooperation should focus on field testing and epidemiology, procedures for standardizing cytologic tests at the clinical level, information exchanges on special techniques in cytology, investigative cytology directed toward clinical application of cytochemistry and immunocytology, and continued effort in the development of cytology automation through the exchange of research information, identification of individuals engaged in cytology research, and the exchange of scientific personnel for information and collaborative research.

Cancer Immunology

The Joint Cancer Immunology Working Group held a 3-day meeting in Hawaii, March 1975, dealing with

"Immunotherapy of Cancer and Its Fundamental Basis." Seventeen scientists discussed immunotherapy with BCG and related material, immunopotentiators other than BCG, immunotherapy with transfer factors or cells, immune evaluation, and other types of immunotherapy.

Interest was expressed in clinical immunotherapy by both sides. As a result it was tentatively agreed that a second conference on cancer immunology be held focusing on the problems and current research in clinical use of immunotherapy.

Cancer Virology

The Joint Cancer Virology Working Group held a symposium on "Recent Advances in Tumor Virology," March 1975, Hilo, Hawaii. The meeting, attended by 7 American and 7 Japanese scientists, enabled the scientists to familiarize themselves with ongoing research on RNA and DNA viruses in each country. Discussions were held on the exchange of experimental materials and information and research areas for future collaboration. Plans are now under way for a joint study of SV 40 mutants. A second meeting on cancer virology is being planned for spring 1976.

Chemical Carcinogenesis

A 3-day seminar, "Protease Inhibitors and Carcinogenesis," took place in Honolulu, Hawaii, March 1975. The seminar concentrated on the effect of a new group of protease-inhibiting compounds, such as leupeptin, antipain, and pepstatin, that exhibit an inhibiting effect on experimental carcinogenesis. Information was exchanged on the biochemical activity of these new compounds, as well as other enzyme inhibitors.

The Japanese working group provided the Americans with generous supplies of the protease inhibitors to be distributed to American cancer researchers for their investigations.

The chemical carcinogenesis groups have planned a U.S.-Japan-Australia tripartite conference on "Modified Cellular and Molecular Controls in Neoplasia" to be held in Hawaii, December 1975. This large conference is being sponsored by the National Science Foundation, the National Cancer Institute, and the Japan Society for the Promotion of Science (JSPS).

High-LET Radiation Therapy

In July 1975 six American radiotherapists and radiation physicists visited several radiation biology and therapy centers in Japan for 7 days. Both joint

working groups discussed the various preclinical and clinical aspects of neutron radiation therapy and reviewed the availability of neutron beam therapy equipment, basic radiation biology, and dosimetry. The joint working groups, sponsored jointly by NCI and the JSPS, are now working on the development of clinical trial protocols for comparative studies.

Exchange of Scientists

Twenty-one JSPS-sponsored Japanese exchange scientists visited from 2 weeks to 6 months the National Cancer Institute and various American laboratories for conferences and definitive collaborative research with American cancer researchers. Five NCI-sponsored American scientists visited Japanese institutions for 2 weeks to observe and survey the development of the Automated Cytology and Instrumentation Program. During April and May 1975, an American scientist was engaged in collaborative research in chemical carcinogenesis at the Institute of Medical Science, Tokyo University.

U.S.-Polish Peoples Republic

Under the agreement between the United States and the Polish Peoples Republic for cooperation in the field of public health, NCI has established a working relation with the Institute of Oncology in Warsaw.

In May 1975 an American exchange scientist visited the Maria-Sklodowska Curie Memorial Institute of Oncology in Warsaw and Krakow. During his stay this individual presented lectures on the clinical aspects of thyroid cancer, one of their continuing research efforts over the years, and consulted with Polish scientists on establishing a new therapeutic and research oncologic center in Warsaw.

In June 1975 another American exchange scientist visited Poland and presented a lecture on the "Progress of Virological Studies in Cancer of Animals and Man" at the Institute of Oncology in Warsaw. Seminars in viral oncology and immunology were also conducted at the branches of the Institute of Oncology in Gliwice, Krakow, Wroclaw, and Poznan.

Potential Agreements with Other Governments

In June 1975 a meeting was held between the director, NCI, and members of his staff with Dr. P. Laudat, Scientific Director for the National Institute of Health and Medical Research (INSERM), Republic of France. Reference was made to the 1974 Martinique meeting between Presidents Ford and Giscard d'Estaing. Dr. Laudat

summarized the interests of the two chiefs of state in furthering American-French cooperation in health, especially in cancer research and cancer control activities. The consensus was that a formal agreement was not necessary, yet there was recognition of the need for expansion and greater participation in the existing NIH-INSERM agreement. Consequently, it was agreed to convene a small U.S.-French strategy group to establish means for effective cooperation that would include workshops on specific cancer problems and the exchange of scientists, information, and research materials.

In May 1975 the NCI director and members of his staff met with a delegation of scientists from the Federal Republic of Germany (FRG), representing the Ministry of Research and Technology, the Society of Radiation and Environmental Research (Munich), and the Cancer Research Center (Heidelberg). The purpose of the mission was to express the interest by the FRG in developing agreements for cooperation in research with specific U.S. agencies (in this case, NCI). The areas of research appealing to NCI and of particular interest to both the Ministry of Research and Technology and the Society for Radiation and Environmental Research are (1) instrumentation for early diagnosis, including pattern recognition and isotope scanning; (2) radiotherapy with high-energy particle emission; and (3) testing plant extracts from the Amazon region for clinical efficacy.

The NCI hosted the visits of two scientific delegations from the People's Republic of China (PRC), sponsored by the Committee for Scholarly Communication under the aegis of the National Academy of Sciences. In November 1974 six Chinese pharmacologists met with NCI staff working in drug development, cancer chemotherapy, and immunology. In May 1975 a delegation of biochemists and molecular biologists from the People's Republic of China were guests of the National Cancer Institute.

A meeting of the U.S.-Egyptian Joint Working Group on Medical Cooperation was held in Washington, D.C., July 1975. There was an exchange of a draft agreement for cooperation between the Ministry of Health of the Arab Republic of Egypt and the Assistant Secretary for Health, DHEW. The draft agreement is being considered by both governments in anticipation of formal joint approval.

Collaborative Research

In accordance with established tradition, the National Cancer Institute during FY 1975 has hosted visiting scientists, associates, fellows, and guest workers from 29 countries, for collaborative cancer research projects with senior NCI investigators. Of these 104 visitors, 20 came from Japan; 11 from India; 7 each from Israel,

Italy, and the United Kingdom; 5 each from Belgium, China (Taiwan), France, and Germany; and the remainder from Argentina, Australia (2), Canada (2), Chile, Czechoslovakia, Egypt (2), Finland, Greece (2), Hong Kong, Korea (2), Malaysia, The Netherlands (4), New Zealand, Nigeria, Norway, The Philippines, Poland (2), Spain, Sweden and Switzerland (3). The scientists and their NCI hosts engaged in fundamental research, environmental research, clinical research, and cancer health services. There is no question of the value of such scientist-to-scientist interaction being the foundation for the development of an eventual comprehensive program of international cooperation in cancer research and research methodology.

Within the purview of the five operating divisions of the National Cancer Institute, 26 grants and 91 contracts were in effect during FY 1975 in foreign countries.

Under the provisions of Public Law 480, the Special Foreign Currency Program, there are nine active cancer research projects in four foreign countries (India, Poland, Tunisia, and Yugoslavia). The thrust of the Yugoslav project is directed toward the study of immunosuppressive and antileukemic activity of pharmacologic agents. Four of the Indian projects are related to chemotherapy, including the screening of indigenous herbal substances as potential anticancer drugs.

To exemplify the benefit of this international collaboration in cancer research, we relate to cancer of the breast, which, at present, is one of the most frequent cancers affecting women in industrialized countries. Thus, under NCI contract the International Agency for Research on Cancer (IARC) in Lyon, France, has organized a special study of this problem in collaboration with the University of Iceland. This study of the whole population of Iceland has been initiated in an attempt to measure the degree of risk that relatives of breast cancer patients face of having breast cancer themselves. Such a study is intended to compare the relative importance of heredity and environment as risk factors in breast cancer.

Studies on cancer of the esophagus are continuing in Iran, again, by the IARC under NCI contract. That this cancer shows wide geographic variation in incidence both between countries and between localized areas within a country such as Iran raises the possibility of identifying the causal factors. The detailed epidemiologic investigation in this study has been completed and the data are being analyzed. Preliminary results indicate a much higher intake of bread in the high-incidence areas than in the low-incidence areas where rice is the staple food. The use of sheep's milk and sheep's milk yogurt was common only in the areas of high incidence. No other foods

or vegetables showed any consistent relationship with the cancer. Small amounts of carcinogens- both N-nitroso compounds and polycyclic aromatic hydrocarbons- were shown to be present in the food samples collected, but the quantities seemed insufficient to explain the very marked geographic variations. The project is continuing with a case control study and with further chemical analyses of food samples for known carcinogens, including mycotoxins.

Liaison with International Agencies

Maintenance of an active association with international cancer research organizations is vital to NCI and the national cancer program. The World Health Organization (WHO) is an organization through whose auspices the public health and medical professionals of more than 140 countries exchange their knowledge and experience on health problems such as cancer. An integral part of NCI's international activities is shared with other organizations such as the International Union against Cancer (UICC), the International Agency for Research on Cancer (IARC), and the European Organization for Research on Treatment of Cancer(EORTC). The fruits of NCI's contribution toward the support of these organizations and agencies are evident from the progress being made in the international arena where effort continues toward achieving the highest possible level of health throughout the world.

The registration of cancer morbidity on an international scale is a prerequisite to studying the significance of geographic variations and distribution. At present, the IARC is collaborating with the International Association of Cancer Registries to collect and publish data under comparable conditions from different parts of the world. The data are stored on magnetic tape in the data-processing unit at WHO headquarters. The morbidity data complement the mortality statistics routinely collected by WHO. Since an internationally acceptable and standardized classification of all forms of cancer is essential for the systematic registration of cancer mortality and morbidity, IARC has been involved in preparing the section on tumors for the next revision of the International Classification of Diseases (ICD), to be published by WHO. Included in this revision as a voluntary option will be a coding scheme for the histologic classification of tumors. This coding scheme is recognized to be of increasing importance in cancer registration, and will be especially valuable for identifying rare cancers which might otherwise be lost in the registration system.

An inevitable feature of epidemiologic studies is the long time taken for them to reach completion and publication. It is thus quite likely that during the period of

a given study, other workers with a similar interest may start collecting similar data. While duplication in epidemiology can provide valuable information, this will only be so if the methods of collecting and analyzing the data are comparable. It is therefore desirable to establish some form of clearinghouse, from where epidemiologists working in different countries could be informed of studies in progress in an effort to avoid unnecessary duplication and ensure that whatever duplication is needed will lead to results that are comparable legitimately. Accordingly, IARC, in association with the German Cancer Research Center, Heidelberg, Federal Republic of Germany, has planned a clearinghouse for current epidemiologic studies and related investigations in high-risk groups, including those subjected to occupational exposures to potential carcinogens.

The coordination of studies in high-risk groups and those subjected to occupational exposures will also contribute to the work of the IARC in preparing its monographs on the evaluation of carcinogenic risk of chemicals to man.

The IARC is actively engaged in collecting, sifting, and evaluating all published data relating to chemical carcinogenicity testing and to epidemiologic studies of the levels of human exposure to chemicals and, where available, of their carcinogenic effects on man. The program has resulted in the publication of IARC monographs on the evaluation of carcinogenic risk of chemicals to man. A total of 160 substances have been scrutinized and the results are included in the six volumes already published.

The selection of substances to be included in the monographs conforms to two criteria. There must be evidence of carcinogenicity of the substance in experimental animals and evidence of human exposure to the substance. The highest priority has been given to assessing those substances for which carcinogenicity in man was suspected. The preparatory work of selecting chemicals and collecting information on them has been carried out in collaboration with the NCI and the Stanford Research Institute.

Under NCI sponsorship, the Committee on International Collaborative Activities (CICA) of the UICC is assisting in the compilation of an International Directory of Specialized Cancer Research and Treatment Establishments, as a service to the international cancer research community. A preliminary edition was compiled for distribution during the International Cancer Congress in Florence, Italy, October 1974. This directory will be compiled now in a comprehensive edition and provisions are included for regular updating. The directory included information on comprehensive cancer centers,

cancer research institutes, university departments or biomedical research centers engaged in a structured program of cancer research, and hospitals or other medical establishments having a separate but identifiable organizational cancer department or unit. This project is an integral segment of the ICRDB program, its source of support.

U.S.-U.S.S.R. Health Exchange

Cardiovascular Portion

The mutual interest in cardiovascular diseases stems from a joint concern about the major threat that these diseases pose to the health of mankind. Heart disease is a health problem of great importance to the peoples of many nations. It is the principal cause of death both in the Soviet Union and in the United States. It has extensive personal and social implications for large segments of the population not only in terms of unexpected deaths but also because it leads to chronic illness and loss of work capability. The solutions to these problems represent difficult scientific challenges. Much more remains to be learned in order to bring these diseases under control. Application of existing knowledge could also decrease illness and death from cardiovascular diseases. It is hoped that the U.S.-U.S.S.R. collaborative program will accelerate progress toward these goals.

The U.S.-U.S.S.R. Joint Program in Cardiovascular Diseases, one area included in the original 5-year agreement between these governments, stresses that "the parties agree to direct their initial joint efforts toward combating the most widespread diseases, such as cardiovascular... diseases, because of the major threat that they pose to man's health." A key element in this agreement that was not included in earlier cooperative programs is the mutual planning and execution of joint research activities in both countries according to an organized work plan and common protocols. A second important innovation is the provision that the mutual cooperation take place directly between specific U.S. and U.S.S.R. health institutions. Thus, the National Heart and Lung Institute of the National Institutes of Health was designated to collaborate with its counterpart institution of the Soviet Academy of Medical Sciences, the A. L. Myasnikov Institute of Cardiology in Moscow.

The individuals responsible for organizing the initial efforts in the joint U.S.-U.S.S.R. cardiovascular research programs were Dr. Theodore Cooper, now Assistant Secretary for Health and then Director of the National Heart and Lung Institute; Professor Eugene Chazov, Deputy Minister of Health of the Soviet Union; and Professor Igor Shkhvatsabaya, Director of the A. L. Myasnikov Institute of Cardiology.

At its first meeting in 1972, the U.S.-U.S.S.R. joint committee selected four programs for initial collaborative efforts in cardiovascular diseases: pathogenesis of arteriosclerosis, management of ischemic heart disease, myocardial metabolism, and congenital heart disease. Since the 1972 agreement, further meetings of U.S. and U.S.S.R. researchers have identified and agreed upon two new areas for joint cardiovascular research: sudden death and blood transfusion, blood components, and prevention of hepatitis, with particular reference to cardiovascular surgery. In addition, an artificial heart research and development program is being developed under a separate agreement signed June 28, 1974, in Moscow.

1. Pathogenesis of Atherosclerosis

Arteriosclerosis, the most common cause of cardiovascular disease, is directly or indirectly responsible for more deaths in the United States and the Soviet Union than any other disease. Because hyperlipidemia is strongly suspected to be a major risk factor in causing premature atherosclerosis and subsequent ischemic heart disease, this subject area was chosen for joint study. Quantitatively, hyperlipidemia is perhaps the most important of the known risk factors for arteriosclerosis. Not only is extreme hyperlipidemia associated with high risk, but even the "average" values believed to be present in American and Soviet populations are associated with higher risks than are the average levels in populations of several other countries.

Automated techniques for classifying hyperlipidemia according to standardized methods have been set up in a number of lipid research clinics (LRC) in the United States and Canada, supported by the National Heart and Lung Institute. The major task of the current network of 12 lipid research clinics is to collect data on the prevalence of arteriosclerosis and information concerning environmental, familial, and genetic influences. It is expected that new standards of "normal" for lipids and lipoproteins for American populations will be set by this study. In addition, an intervention trial is under way in the United States to determine the beneficial effects of treatment of hyperlipidemia.

Through the U.S.-U.S.S.R. agreement this continentwide study has been expanded to encompass an extensive comparison of the nature and magnitude of the arteriosclerosis problem in the United States and in the Soviet Union. Combining the data from the U.S. clinics and the recently established U.S.S.R. clinics will significantly broaden the inferences and conclusions that can be drawn from the study.

The U.S.-U.S.S.R. study which involves large numbers of individuals (men, 40-59 years old) in the two countries who are being studied according to carefully developed common research protocols, intends to compare the prevalence of hyperlipidemia and ischemic heart disease in the United States and the U.S.S.R. In the United States the lipid research clinics program expects to study approximately 22,000 individuals in the initial phase (phase 1) of the study; and from 3,000 to 5,000 in the second, more specialized, phase of the study (phase 2). In the U.S.S.R., the study is being conducted in Moscow and Leningrad. 10,000 individuals will be studied in phase 1 and approximately 2,500 in phase 2.

This program has been the most active program in the cardiovascular portion of the U.S.-U.S.S.R. health agreement since its beginning. From the time of the signing of the agreement on these studies, collaboration in this area has been directed toward the achievement of standardization and unification of epidemiological and biochemical methodology. During the past year significant progress was made toward achieving these goals. In July 1974 a U.S. delegation visited the Soviet Union to review the progress in the cooperative study and the pretrials that had just been completed in the clinics in Moscow and Leningrad and to resolve any difficulties that may have arisen since the last joint meeting. The delegation included five members of the joint U.S.-U.S.S.R. steering committee and five members of the working group.

General issues on which agreement was reached included a specific timetable with deadlines for each sequential step leading to the formal study. U.S.S.R. representation at meetings of the LRC directors and the U.S. Prevalence Subcommittee was agreed to be desirable. Provisions were made to improve the communications network and to transmit data via telex until the Soviet computer system can be developed and made operational. To institute regular contact, it was agreed to exchange monthly reports.

In the biochemistry area, laboratory standardization and quality control procedures were reviewed and clarified where necessary. Tests for determining secondary causes of hyperlipoproteinemia were discussed, and it was agreed that each clinic would conduct its own tests, using identical methodology, reagents, and standards. A certain number of split samples would be exchanged by the two laboratories to maintain comparability. In addition, the Center for Disease Control, Atlanta, will provide quality control pools and primary standards for secondary tests.

The epidemiology working group reviewed and defined U.S.S.R. procedures for selecting the population sample. In addition, significant discrepancies between the U.S.

and U.S.S.R. forms were discussed and amended. Plans were made to initiate and test the exchange of study data.

Training and certification procedures for U.S.S.R. dietitians were formalized. Four dietitians were certified during the visit. Agreement was reached on quality control procedures for monitoring the coding of nutritional data.

In the cardiology area, it was agreed that the U.S.S.R. clinics would conduct the graded exercise test using the treadmill. This will ensure comparability of cardiological data. Agreement was also reached on the procedures for conducting resting and stress ECG tests and for coding ECG recordings.

Two Soviet scientists visited the United States in November 1974 to attend the meetings of the Arteriosclerosis Council of the American Heart Association and to represent the Soviet lipid research clinics at the fall 1974 meeting of the U.S. lipid research clinic directors in Dallas, Texas. Key items of the study were discussed in biochemistry, nutrition, epidemiology, and cardiology. A number of lingering problems in each area were reviewed.

A U.S. working group visited the U.S.S.R. in March 1975 to finalize preparation for the formal U.S.S.R. prevalence studies. At the time of the visit, the Leningrad LRC was completing its pilot study, having successfully passed laboratory standardization in January. During the visit, the working group reviewed preliminary pilot data from Leningrad and visit 1 screening procedures at both clinics. It was confirmed that the Moscow laboratory had passed the standardization program.

Training and certification of all interviewers is now complete. ECG certification forms and tapes have been completed in both clinics. The principal milestones in the two Soviet lipid research clinics since the March visit include (1) completion of pilot studies in both clinics, (2) initiation of visit 1 of formal study, and (3) initiation of visit 2 of formal study.

Two senior U.S.S.R. scientific workers visited the United States in 1975 for 2 months. Their visits included work at the laboratories of the Molecular Diseases Branch, NHLI, and the Center for Disease Control. They also attended the lipid research clinics directors' meetings in Bethesda, as well as the meetings of the American Society for Clinical Investigators in Atlantic City.

2. Management of Ischemic Heart Disease

While problem area 1 deals with the very important subject of defining ischemic heart disease and its association with environmental and inherited factors in that large portion of the populations in both countries who are at risk of developing heart disease, problem area 2 is concerned with a second large segment of the populations in the U.S., U.S.S.R., and worldwide who are already victims of the disease. This research is patient-oriented and seeks to find ways to minimize mortality, morbidity, and suffering.

In the United States, the surgical technique under study uses a blood vessel graft to bypass a narrowed or occluded segment of a coronary artery. Although over 25,000 such operations are done annually in the United States for treating chronic disability from angina pectoris and heart attacks, the indications for and the effects of coronary artery surgery in the treatment of coronary heart disease remain to be determined. While coronary artery surgery is very popular in the United States, this method has received little following in similar patient populations in the U.S.S.R. Conversely, some of the medical approaches in the U.S.S.R. are unfamiliar to U.S. heart specialists.

Through the U.S.-U.S.S.R. agreement a collaborative study is being developed that takes advantage of this unique opportunity to systematically assess and compare the way well-defined heart disease patients are treated in the two countries. The ultimate goal of this coordinated study is to assess various medical versus surgical therapies for the treatment of ischemic heart disease. These therapies include "differential" intensive medical management in the U.S.S.R., "conventional" standardized medical management in both countries, and coronary bypass surgery in the United States.

Between 1972 and 1973, initial agreement was reached on methodological bases of the U.S.-U.S.S.R. joint study, such as the criteria for patient selection, patient examination, therapy, and assessing the effectiveness of treatment. Pilot studies have been completed both in the United States and the Soviet Union. Since then, U.S. and U.S.S.R. cardiologists and cardiovascular surgeons have met repeatedly to further define criteria for the selection of patients who will receive differential medical treatment and to develop specific work plans for the various phases of the joint study. An exchange of fellows also took place in 1973 and 1974.

Well-defined patients, that is, patients who both the American and Soviet physicians are in complete agreement concerning the state of their coronary artery diseases, will be placed in one of three groups. Two "intensively treated" groups and one "reference" group, will be composed of men, 30 to 60 years of age.

In the United States, patients who have one or more coronary arteries occluded by lesions causing greater than 70 percent obstruction will be treated surgically. In the Soviet Union, the method of treatment for patients with identical heart disease will be entirely nonsurgical. It will consist of a combined drug therapy and exercise program carried on in the hospital and, after discharge, in a health resort.

It is anticipated that the end points for the joint study will occur in 5-8 years. Two years are required for patient intake. A subsequent 5 year follow-up period plus 1 year for data analysis is anticipated. During the 5-year follow-up period the patients in the U.S.-U.S.S.R. international study will be examined periodically to evaluate the effectiveness of their respective therapies.

From May 26 to June 7, 1974, a U.S. delegation visited the U.S.S.R. to review the progress and to develop further plans for the upcoming year. The overall study design and the protocol of February 1973 were reviewed in detail. Specific task forces also met on angiography and electrocardiography. Although modifications in the detailed protocol were largely clarifications, some specific modifications - such as the elimination of the requirement for a specific number of anginal attacks per week, angiographic and ventriculographic characterization of patients in the intensively managed group, elimination of the requirement that the conventional medical management include only the intermittent use of such agents as long-acting nitrates and propranolol, and a decrease in the frequency of required follow-up - were advanced. A memorandum of understanding was drawn up, detailing the future plans of collaboration.

A reciprocal visit by a Soviet delegation to the United States, October 25 through November 7, 1974, enabled scientists to review experiences in the pilot studies in the Soviet Union and in the United States, to further clarify plans and protocols, and to develop plans for the future. Based on experiences of the domestic studies in each of the two countries and the international U.S.-U.S.S.R. plans, all of which were in advance development stages, opportunities for improvements in each of these plans became evident. In addition, record forms were exchanged that will serve not only to develop the international U.S.-U.S.S.R. study, but to aid each of the two domestic

studies in their future development. Particular attention was paid to the analysis of coronary angiograms, review of electrocardiograms, and patient follow-up.

Since the October 1974 joint meeting, communication has been maintained between the U.S.-U.S.S.R. coordinators in order to complete collaborative plans in a timely fashion. In May 1975 the U.S. coordinator forwarded information to the U.S.S.R. on the pilot phase of the U.S. studies, as well as an extensive document containing the plans for the definitive U.S. study. These plans had just been reviewed by a U.S. advisory group at that time and formally approved by the National Heart and Lung Institute.

In preparation for the September 21 - October 3, 1975, U.S.S.R. visit by a U.S. delegation, the United States has prepared copies of angiograms for joint viewing to further U.S. and U.S.S.R. standardization of angiographic interpretation. Also, a computer program that will print out the data from the domestic U.S. study in the sequence of the U.S.-U.S.S.R. international study is being developed. It is expected that results of this effort will be available for the September meeting.

3. Myocardial Metabolism

A fundamental understanding of the structure and function of the heart muscle is crucial to the development of improved methods of prevention and therapy for heart disease. Specifically, it is important to search for therapies that will enable the heart muscle to survive a heart attack and to develop methods that may prevent additional heart muscle damage.

The role that this research project will play in future cardiovascular programs is likely to be a very important one, both in terms of joint development of new therapies and methods of prevention. Research areas currently being addressed by Soviet and American scientists include the manner in which heart muscle cells obtain energy, regulate their growth, coordinate their contractions, and respond to induced alterations in their environment. These studies entail basic exploration at the most sophisticated levels of modern medical science, including physiology, molecular biology, biochemistry, and biophysics.

Because of this inherent complexity and specialization, it is difficult to identify areas where major collaborative research projects can be carried out in the immediate future. However, the regular and constant reporting of research results and the exchange of technical information

can be of invaluable assistance to researchers in the United States and the U.S.S.R. in their common goal to prevent and control heart disease. To accelerate this exchange of information, under the joint exchange agreement, a symposium was held in the United States in November 1973. Extensive discussion of many different research projects relating to myocardial metabolism led to the identification of new leads and ideas that will serve as the basis for future collaborative efforts. Significant advances in the understanding of myocardial metabolism were identified, which demonstrated the high level at which this research is conducted both in the United States and the Soviet Union.

The proceedings of the symposium have been published in English as a supplement of the journal Circulation Research. The proceedings have also been published in Russian in the Soviet Union. Arrangements have been made for the regular exchange of important research reports for mutual publication on a regular basis. Professor Chazov's book, Myocardial Infarction, has been translated into English under the auspices of the National Library of Medicine and the National Heart and Lung Institute and will be published in the United States in the near future.

Three U.S. exchange fellows spent extended periods of time working in Soviet laboratories in the area of myocardial metabolism. Dr. Rannels and Dr. Shell worked mainly in the myocardial research laboratories at the Myasnikov Institute of Cardiology in Moscow, but visited cardiovascular institutes in other Soviet cities as well.

In the spring of 1975, Dr. Muller from the Department of Medicine, Harvard Medical School, spent 3 months in the U.S.S.R. His project was an intensive joint U.S.-U.S.S.R. clinical study of the effect of hyaluronidase on reducing infarct size in man. Although complete analysis of the data of this study has not been made, preliminary analysis appears to support the hypothesis that hyaluronidase treatment reduces infarct size.

Dr. Saks, senior scientific worker at the Myasnikov Institute of Cardiology, visited the United States as a Soviet fellow in the spring of 1975. His program included visits to the Laboratory of Cell Biology, National Heart and Lung Institute; the Johnson Research Foundation at the University of Pennsylvania in Philadelphia; the Milton S. Hershey Medical Center, Pennsylvania State University; Johns Hopkins School of Medicine; the Cardiovascular Research Laboratory, UCLA Medical Center in Los Angeles; and the Department of Physiology, University of California at Berkeley. In addition he attended several scientific meetings. Dr. Saks, and one of the U.S. exchange fellows, Dr. Shell, have completed a research

paper as a result of their collaborative research in Moscow; the paper, "Studies of Mechanisms of Energy Transport in Heart Cells", will be published in Circulation Research in 1975.

In June 1975 a second Joint Symposium on Myocardial Metabolism was held in the Soviet Union to promote further exchange of the latest information in this important area of research. During the joint discussions in Sochi, both sides agreed that as a result of the U.S.-U.S.S.R. collaborative efforts initiated following the 1973 U.S.-U.S.S.R. symposium in Ponte Vedra, particularly the exchange of young scientists from both countries, important new lines of joint research have been outlined of potential benefit to the people of the United States and of the Soviet Union. The following studies were completed or are in progress: clinical studies aimed at limiting the extent of damage to heart muscle following myocardial infarction, studies of the regulation of protein synthesis and degradation in the myocardium, studies of energy transport in the myocardium, and properties of creatine phosphokinase from heart muscle.

The topics discussed included disturbance in the function of the heart muscle in patients with ischemic heart disease, the effect of hormones and drugs on normal and ischemic heart muscle, changes in the blood circulation to the heart during ischemia, energy processes in the heart muscle, and possible clinical applications of the results of these basic studies. The proceedings of the symposium will be published in Russian in the Soviet Union and in English in the United States.

4. Congenital Heart Disease

Congenital heart disease is an important disease of children and young adults, both in the United States and in the Soviet Union. In the United States, about eight of every 1,000 children are born with this disease.

There are many types of congenital heart defects. Each may occur alone, or in combination. Less than 3 percent are known to be related to a particular event or disorder occurring during pregnancy, such as rubella infection, or the use of certain drugs. Thus, in the great majority of cases congenital heart disease cannot as yet be prevented and, therefore, the only hope for these children is therapeutic measures to correct or control their heart disease.

Congenital heart disease may cause considerable impairment of the quality of life of the patient surviving

into adulthood. Fortunately, approximately 80 percent of infants with this disease can now be cured or helped with corrective surgery. These surgical successes are now being expanded by the development of diagnostic and surgical techniques applicable to the newborn.

The objectives of the U.S.-U.S.S.R. collaboration in this research area are to explore new methods of diagnosis and postoperative care in order to further reduce mortality from congenital heart disease and to improve the surgical treatment of complex heart defects. It is hoped that through the exchange of information in this problem area, Soviet and American surgeons will be able to achieve a higher rate of success in corrective surgery of congenital heart defects. The proceedings of the second joint symposium will be published by the Soviets in both English and in Russian. It is expected to be published in the first quarter of 1976. The United States was responsible for the editorial review of the English version of the proceedings. The proceedings will be distributed to the U.S. and U.S.S.R. participants and all interested scientists.

5. Sudden Death

Fifty percent of all deaths from coronary heart disease occur suddenly. Sudden death coronary arteriosclerosis may occur in individuals with no symptoms of heart disease, in patients with angina pectoris, in patients with a history of heart attacks, and during an acute heart attack. The immediate mechanism of sudden death is believed to be a disturbance in the rhythm of the heart.

The topic of sudden cardiac death is of major concern to scientists in the United States. A series of studies have been undertaken to identify factors that precipitate, or "trigger", acute heart attacks in patients with coronary arteriosclerosis. It is hoped that these studies will help to elucidate factors in the person or his environment that make him highly susceptible to potentially lethal heart attacks and to discover premonitory signs and symtoms that may warn the patient or his physician of an impending attack in time to take preventive measures or to hospitalize the patient before the onset. Other studies have involved the identification of factors that cause or contribute to a quickly fatal outcome after onset and the development of practical methods for treatment of the very early stages of the acute heart attack in an effort to lessen the risk of sudden death.

The avoidance of sudden death from cardiac arrhythmia is a very important area of study for any collaborative

efforts to reduce coronary heart disease mortality. Soviet and American physicians alike are looking for effective ways to deal with the problem.

The area of sudden death was one of the new cardiovascular program areas approved under the official agreement at the annual meeting of the Joint U.S.-U.S.S.R. Committee for Health Cooperation in 1973. A. U.S. delegation visited the Soviet Union in the fall of 1973 to discuss the development of initial plans for collaboration in this area. Soviet and American scientists exchanged information and held extensive discussions on the following topics: the magnitude of the sudden death problem in both countries, risk factors for sudden death, the relationship between arrhythmias and sudden death, current approaches to management of sudden death in the United States and the Soviet Union, emergency treatment that might be useful in controlling arrhythmias, suggestions for joint U.S.-U.S.S.R. projects, and the development of mechanisms for ongoing exchange.

In contrast to problem areas 1 and 2, at the initiation of this area of collaboration, there were no current or projected large-scale collaborative activities in either the United States or the Soviet Union. A number of pilot studies were in progress in the United States. The immediate task of both the United States and the Soviet Union was to rapidly assess the current state of the art and to form interested and competent working groups to explore current activities and future opportunities for joint research in sudden death.

U.S. scientists interested in and working in the area of sudden death met in the fall to exchange current information on the relationship between arrhythmias of the heart and sudden death. The proceedings of this meeting will be published shortly and will be made available to the Soviet scientists in problem area 5. Also in the fall of 1974 the National Heart and Lung Institute, in collaboration with the Division of Computer Research and Technology, sponsored a conference on computers in cardiology. The topics discussed during this conference have direct relevance to this problem area, and the proceedings of the conference have been forwarded to the Soviet scientists engaged in the U.S.-U.S.S.R. collaborative activities in sudden death.

To move ahead in this area, the United States has provided U.S.S.R. scientists with monitoring equipment for the joint study. Shortly after the third joint committee meeting, the U.S.S.R. reported that four Soviet physicians had already been trained to operate the equipment. However, Professor Lukomsky's untimely death post-

poned any possible expansion of collaborative activities, and the U.S.S.R. has requested a delay in initiating the collaborative effort. In January 1975, the Soviets reported having difficulty with the monitoring equipment provided by the United States and requested U.S. assistance in analyzing the problem. A series of magnetic tapes were forwarded to the U.S. coordinator for analysis.

A U.S. delegation visited the U.S.S.R. in June 1975 to review program plans and to develop a plan for the upcoming U.S. visit by a Soviet delegation. The major discussions of activities in this problem area were held at the Myasnikov Institute of Cardiology. The delegation also visited the Institute of Cardiology in Tbilisi. The Soviets have made a definite new commitment in the area of joint work on sudden cardiac death. A decision has been made to expand joint collaboration with the Myasnikov Institute to involve cardiology institutes in Kaunas, Lithuania, and Tbilisi, Georgia, thus moving the collaboration toward a truly national Soviet effort in this problem area.

The U.S. coordinator presented an overview of sudden cardiac death studies in the United States. Like the United States, the U.S.S.R. is also pursuing two main directions of research in sudden death: basic studies of sudden death and public health programs aimed at identifying the population at risk.

Some of the most recent work in the area of sudden cardiac death in the United States has been detailed, such as determination of the prevalence of ectopic activity in the population and qualitative and quantitative relationship of this ectopic activity to the major risk factors being studied in the multiple risk factor intervention trial population.

During its visit, the U.S. delegation was informed by the U.S.S.R. scientists that there had been considerable delay in initiating the joint studies with the monitoring equipment provided by the U.S. Apparently, the Myasnikov Institute where the studies were to have been performed had been closed for about a year. It was only in January 1975 that the 24-hour monitoring study could be started. The current studies are on patients who have had a myocardial infarction, conducted in accordance with the protocol previously agreed upon in joint discussions with the United States. The purpose of task 1 is to determine the prevalence of arrhythmias in patients and the relationship to sudden death. This task is being implemented. Task 2 on the U.S.S.R. side will be concerned with the epidemiology of sudden death. It will be conducted in healthy people, in people with risk factors, and in people with

ischemic heart disease. The purpose of task 2 is to determine the correlation and identify specific conditions for increased trends of sudden death. U.S. monitors and analyzers will be used only for task 1.

The current plan for U.S.S.R. task 1 is for the Myasnikov Institute to monitor 400 patients a year for 3 years and for the cardiology institutes in Tbilisi and Kaunas to monitor 100 patients a year each. These patients will also be monitored for 3 years.

The U.S. coordinator met with the Myasnikov staff directly involved in the monitoring study to review accumulated data. He also reviewed in detail the U.S.S.R. magnetic tapes submitted to the U.S. for analysis. Detailed reports were left with the Soviet scientists for their study and comparison.

The U.S.S.R. is continuing the study of the relation of ventricular ectopic activity to risk of sudden death in patients with ischemic heart disease, using the equipment provided by the U.S. for monitoring and analyzing the data. U.S. scientists have agreed to provide technical consultation as needed.

U.S.S.R. and U.S. scientists are also proceeding as planned with studies of frequency of different types of ventricular ectopic activity in selected high-risk populations and in the general population and have agreed to exchange results from these studies.

6. Blood Transfusions, Blood Components, and the Prevention of Hepatitis in Cardiovascular Surgery

The past two decades have witnessed rapid advances in the use of blood for therapeutic purposes. High-quality blood and blood products are essential for the effective treatment of many diseases. To give the patient enough of what he needs and when he needs it requires recruiting donors, collecting the blood, separating it into its components, detecting and eliminating disease-causing agents, matching the components for compatability, and administering the blood to the patient in a failsafe manner.

The problem of blood transfusion, blood components and prevention of hepatitis, with particular reference to cardiovascular surgery, was approved as a new problem area in 1973, at the joint U.S.-U.S.S.R. committee meeting. The problem area not only provides a link between our two countries in an area of mutual interest and needs, but it also promotes the collaboration of internists and surgeons who may view the problems of blood management from different perspectives.

A U.S. delegation made a preliminary visit to the U.S.S.R. in December 1973; a reciprocal visit by a Soviet delegation was made to the U.S. in October 1974. The U.S.S.R. delegation visited many important blood centers and laboratories in the United States: The New York Blood Center, the International Hemophilia Training Center at Mt. Sinai Hospital in New York, the Ortho Diagnostics' research laboratories and production facilities in Raritan, the NIH Clinical Center Blood Bank, laboratories at the Bureau of Biologics of the Food and Drug Administration, and the American Red Cross.

The second joint U.S.-U.S.S.R. working meeting in this problem area was held at the National Institutes of Health, October 21-23, 1974.

The delegation adopted two major themes for collaborative scientific investigations: approaches to the prevention of hepatitis in blood transfusion, particularly in cardiovascular surgery and the use of whole blood, blood components, blood derivatives, and blood and plasma substitutes with particular emphasis on cardiovascular surgery.

To approach this collaborative effort in a well-organized manner, the U.S. and U.S.S.R. coordinators exchanged in January 1975 lists of principal centers in each country engaged in research in the identified subject areas. In March 1975 the coordinators exchanged preliminary plans for implementing projects in the two major themes. Discussions of these preliminary plans will be held during the September 1975 U.S.S.R. visit of a U.S. delegation. The key element in the development of these joint projects is the exchange of young health specialists who will actively participate in evolving the program. It is anticipated that the first exchange of U.S. and U.S.S.R. health specialists in this area will begin at the end of 1975 or early 1976.

Artificial Heart Research and Development

In June 1974 after 2 years of exploratory discussions and exchanges, the governments of the U.S. and the U.S.S.R. signed an agreement designating the field of artificial heart research as a new area of cooperation. The U.S.-U.S.S.R. agreement in artificial heart research and development provides for joint efforts in research on, and the development and testing of devices, materials, instruments, and control mechanisms that will provide cardiovascular support, including total heart replacement.

Present and foreseeable techniques of general and pharmacologic management of acute and chronic heart failure or shock still leave a substantial fraction of patients with compromised or fatally impaired heart function. By supportive mechanical devices, it is possible to assume some of the pumping function of the heart and to relieve its work load. At present, such techniques are applicable for brief periods in man and have been employed for longer periods in experimental animals. For example, recent studies of patients in the United States have shown a definite reduction in the amount of heart muscle damaged from heart attack when the heart is assisted during recovery by means of a device called the intraaortic balloon.

Partial and totally implantable heart assist devices may be of significant use in the future for the correction of acute and chronic heart failure. In recent studies in the United States a device to assist the left side of the heart has performed successfully in experimental animals. Mechanical techniques for augmenting or substituting for the performance of the heart must be expanded to encompass emergency temporary devices for short-term management, extracorporeal assist pumps for intermediate periods of use, long-term implanted heart assist devices, and total artificial hearts.

Related opportunities and needs exist both to explore the function of assisted circulation and to develop and improve various components of circulatory support systems. These components include compatible biomaterials, pumps, actuators, energy transforming devices, implantable energy systems, transcutaneous energy transmitters, and control systems for the devices.

A U.S.S.R. delegation, headed by the U.S.S.R. Minister of Health, Boris Petrovsky, visited the U.S. in October 1974 to develop plans for implementing this intergovernmental agreement. The major collaboration efforts agreed upon in the October memorandum of understanding were familiarization and exchange of technical aids and devices from each side; the holding of a joint conference in 1975; and preparation for a future exchange of samples of artificial heart devices, circulatory assist devices, and their subcomponents.

Early in 1975, names of key U.S. and U.S.S.R. institutes planning to participate in this exchange were telexed by each side. In April a Soviet delegation visited the U.S. to further develop collaborative efforts initiated in October 1974. In addition, the U.S.S.R. delegation had an opportunity to attend the annual meeting of the American Society for Artificial Internal Organs,

participate in the ASAIO international workshop on artificial internal organs, and visit several U.S. scientific institutes specializing in the development of circulatory assist devices and the total artificial heart.

A joint U.S.-U.S.S.R. meeting was held on April 28 and 29, 1975, to develop a new memorandum of understanding under this agreement. The major items discussed were scientists to participate in the program; exchange of these scientists, equipment, and joint protocols; inclusion in program of joint research and development of circulatory assistance; exchange of lists of devices and technical aids related to artificial heart and circulatory devices; and joint publication of results of studies and evaluation.

Fellowships, Contracts, Grants

During FY 1975, the National Heart and Lung Institute funded six foreign fellowships, eight foreign contracts, and ten foreign research grants. In addition, NHLI supported seven research grants with foreign affiliations.

International Meetings and Visitors

All divisions of the National Heart and Lung Institute (NHLI) have sent personnel to numerous international scientific meetings. NHLI staff members have actively participated in these meetings by presenting papers, being discussion panelists, or representing the NHLI at the meetings. A brief description of some of the meetings follows.

Division of Heart and Vascular Diseases

During FY 1975, a majority of the division's professional staff participated in international meetings, among which were the Meeting of the American Society for Pharmacology and Experimental Therapeutics held in Montreal, Canada; the Fifth International Symposium on Drugs Affecting Lipid Metabolism, Milan, Italy; the Canadian Cardiovascular Society Meeting in Vancouver, Canada; the International Symposium on Lipids and Heart Disease, Stockholm, Sweden; the First International Congress on Twin Studies in Rome, Italy; Symposium on Hyperlipidemia and Coronary Artery Disease, Tel Aviv, Israel; and the WHO Meeting on the Effectiveness of Treatment in Mild Forms of Hypertension, Madrid, Spain.

Division of Lung Diseases

The staff of the lung division was actively involved in many international meetings in FY 1975. These included

the International Congress of Physiology and Satellite Symposium held in New Delhi, India; the WHO Workshop on Epidemiology of Nonspecific Respiratory Diseases in Geneva, Switzerland; the International Conference on Lung Disease sponsored by both the American and Canadian Thoracic Societies and held in Montreal, Canada; and the International Conference on Membrane Lung Technology and Prolonged Extracorporeal Perfusion in Copenhagen, Denmark.

Division of Blood Diseases and Resources

Examples of international meetings attended by staff members in this division during FY 1975 include the Twenty-Fifth Congress of International Society of Hematology, Jerusalem, Israel; Symposium on Fibrinolysis held in Montreal, Canada; and the International Committee on Thrombosis and Haemostasis in Basel, Switzerland.

Division of Extramural Affairs

The Director of the Division of Extramural Affairs attended the Twelfth International Congress on Diseases of the Chest held in London, England.

Division of Intramural Research

The staff of the Division of Intramural Research was very active in international scientific meetings during FY 1975. Many staff members attended more than one international meeting to discuss their own research findings and to learn about research by scientists in other countries. Examples of some of the many meetings attended by the DIR staff include the Second International Conference on Cyclic AMP, Vancouver, Canada; symposium in honor of Dr. Fritz Lipmann held in West Berlin, Germany; the second International Workshop on the Human Gene Map in Amsterdam, Netherlands; the Second Congress of Immunology, Brighton, England; the Fifth Parathyroid Conference, Oxford, England; the Laurentian Hormone Conference held in Mt. Tremblant, Canada; the Pan American Symposium on Vasoactive Peptides and Hypertension, Mendoza, Argentina; the Twenty-Fifth Congress of the International Society of Hematology held in Jerusalem, Israel; the Seventh World Congress of Cardiology, Buenos Aires, Argentina; the Fourth International Congress on Hormonal Steroids, Mexico City, Mexico; the International Congress of Lipid Biochemistry held in Milan, Italy; the Fifth International Symposium on Olfaction and Taste, Melbourne, Australia; the South American Congress on Pharmacology, Lima, Peru; the Fourth Workshop on Experimental Liver Injury on Pathogenesis and Mechanisms of Liver Cell Necrosis, Freiburg, Germany; and the International Congress of Nephrology held in Florence, Italy.

General

In addition, the institute has had representatives at the following meetings dealing with international research: Conference between the Royal Society of Medicine of England and the Fogarty International Center (FIC) of NIH to discuss proposals for future Anglo-American conferences; Meeting of the Honorary Board of Trustees of the Miguel Servet Fund of Spain; FIC's Conference on International Health Costs and Expenditures at NIH; and the International Conference on Women in Health.

During FY 1975 there were numerous international visitors to the National Heart and Lung Institute. Some of these visiting foreign scientists included the U.S.S.R. Minister of Health, Boris Petrovsky; Dr. Katsumi Meguro, Deputy Chief, Medical Affairs Division, Ministry of Health and Welfare, Japan; Dr. Z. Pisa, Chief, Cardiovascular Diseases, World Health Organization, Geneva, Switzerland; and Dr. Lie, Chief of Cardiology at the General Hospital in Jakarta, Indonesia. Also, NHLI staff discussed the institute's programs with a number of visiting foreign scientific writers.

Proposals For Future International Programs

Proposals for future collaborative health research with Brazil, Germany, India, and Poland were submitted to the Fogarty International Center (FIC) in FY 1973 for consideration. Action on three of these proposals is still pending.

During FY 1974 the National Heart and Lung Institute responded to inquiries from FIC concerning possible U.S.-Argentina collaboration in the cardiovascular area.

In FY 1975, several discussions were held between the staff of the National Heart and Lung Institute and representatives of the Federal Republic of Germany (FRG) to consider proposals for collaboration between U.S. and FRG scientists. A summary of discussion between these two countries was developed jointly and formally signed. A workshop on artificial circulatory support, with particular emphasis on the area of biomaterials development, testing, evaluation, and the use of biomaterials in circulatory devices will take place in FRG in FY 1976 and will be attended by three American experts. At the conclusion of this workshop, future plans for collaboration in the field of artificial circulatory support will be discussed.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

The mission-related diseases of the National Institute of Allergy and Infectious Diseases (NIAID) include many that constitute insignificant health problems in the United States but have a large impact on the socioeconomic and health status of populations of many countries of the world. The international benefits of the NIAID research programs are of two categories: studies conducted in U.S. laboratories on diseases of importance mainly to other countries and studies conducted abroad that are either funded by the institute or carried out in collaboration with U.S. scientists.

In addition to the ubiquitous maladies, such as hepatitis, tuberculosis, and the allergic, respiratory, enteric, and sexually transmitted diseases, the NIAID programs support research on most of the bacterial, fungal, viral, and parasitic diseases that create large problems in the tropical and subtropical countries of the world. Those diseases include leprosy, cholera, dengue, onchocerciasis, filariasis, trypanosomiasis, leishmaniasis, schistosomiasis, malaria, and biologic control of the vectors of disease. Probably the most significant contributions stem from the extensive program for research in immunology that supplies information on the disease mechanism and new and improved methods for diagnosis, treatment, and prevention.

Foreign research grants, while relatively few in number, are of high caliber, having successfully competed with a large number of other grant applications, many of which are approved but unfundable at current budget levels. These include grants to foreign institutions, grants to U.S. institutions that fund part of the investigators' studies abroad (e.g., ICMR program), and collaborative research funded in certain countries with U.S.-owned local currency. During FY 1975, 17 research grants were made to investigators in 10 countries. The bulk of that funding (72.3%) was for studies in immunology. Grants awarded to U.S. investigators for training abroad were largely (65.7%) in the field of immunology.

Tabular data on U.S. domestic research grants that fund a portion of the studies are not readily available. Funding of this type enables the research investigators to conduct studies in areas where the diseases under study are prevalent or endemic, but rare or nonexistent in the United States. The nature of such studies can be illus-

trated by the following examples of studies conducted by NIAID intramural scientists. They also illustrate some of the studies on diseases of prime importance to other countries.

Malaria

A videotape technique for study of the invasion of red blood cells by malaria merozoites led to immunochemical studies of the surface receptors involved. Based on previous observations that Duffy negative blood group West Africans had greater resistance to Plasmodium vivax malaria, Duffy positive and negative red cells were used in an in vitro system with P. knowlesi, to reveal that Duffy positive red cells were invaded, whereas the Duffy negative cells were resistant. In addition, removal of Duffy blood group determinants by proteolytic enzymes, or blocking the receptors with anti-Duffy serum, markedly reduced invasion. These findings open the way to a search for similar type receptors for other species of malaria and possibly to exploitation of this knowledge for approaches to rendering red cells resistant to merozoite invasion as a method of treatment or prevention of malaria.

As a WHO short-term consultant, Dr. David J. Wyler (LPD/NIAID) spent nearly 4 months in Gambia, West Africa, studying aspects of the cell-mediated immunity in malaria. Cases of falciparum malaria were found to have significantly reduced circulating T cells during acute infection. The finding of a chemotactic factor for monocytes in splenic extracts of mice and monkeys with malaria may help to explain why splenomegaly is so prominent in malaria. A review of old data on the influence of splenectomy upon the course of established P. inui infections in monkeys has revealed an interesting observation that splenectomized animals cure themselves in contrast to intact animals that have chronic infections for many years.

Filariasis

In collaboration with the health authorities of the Cook Islands, South Pacific, who had scheduled antifilarial drug treatment of the population of the out island of Mauke, Drs. Eric Otteson, Louis Heck, and Peter Weller (LCI, LPD/NIAID) spent 4 months on the island conducting clinical and immunologic studies before, during, and after the mass treatment. Through cooperation provided by Duke University and TIB/NIAID, Marilyn MacQueen joined the field team and conducted HL-A typing of a large portion of the study population. The establishment of a field laboratory on Mauke enabled the performance of function tests and those possible only with fresh material. Many specimens were collected and preserved for serologic

and biochemical analysis in the Bethesda laboratories. This expedition provided an invaluable opportunity to correlate the laboratory and clinical observations of this disease and to observe the dramatic effect of diethylcarbamazine in clearing the circulating microfilaria; 90% reduction of worms in the first hour of treatment. Additional studies were done on the dog, rodent, and mosquito populations of the island.

Dengue and Other Virus Infections

The Pacific Research Section, LPD/NIAID, located in Honolulu, Hawaii, is the center for a variety of collaborative studies and laboratory reference from many of the islands and countries in the Pacific area. These studies provide expert help to the health authorities of those areas and some unique research opportunities for Dr. Leon Rosen and his staff of research scientists at the Pacific Research Section. The following are examples of such studies.

Dengue type 1 virus reappeared after 30 years on the Pacific islands of Nauru, Ponape, and Fiji, affording an opportunity to study the behavior and manifestations of this virus under relatively simple and known epidemiologic conditions. Studies were done, also, on a flare-up of dengue type 2 disease on Tonga and Tahiti. It was observed that the fatal form of the disease (hemorrhagic and shock syndrome) can result in individuals who have not previously experienced dengue infections. In collaboration with the SEATO laboratory in Thailand, it was demonstrated that two to three times as many virus isolations were obtained from dengue hemorrhagic fever patients by mosquito inoculation than by conventional cell culture techniques. Studies of oral susceptibility to dengue virus among geographic strains of the vector mosquito Aedes albopictus disclosed a similar pattern with all four dengue serotypes. Studies on genetic differences in susceptibility of mosquito strains showed that significant changes resulted from selective inbreeding, but no clear-cut mode of inheritance could be determined. A simple direct feeding technique was developed to test the ability of mosquitoes to transmit dengue viruses without feeding on a vertebrate host.

Serum surveys of Southeast Asia and Pacific islands have shown that human Chikungunya virus infections are confined to the mainland, Indonesia, and The Phillipines. However, antibodies to another group A arbovirus, Ross River, were found in serum specimens from New Guinea and the Bismarck and Solomon islands. Using a plaque reduction neutralization test, evidence of human infection

with four Phlebotomus (sandfly) fever group viruses was found in specimens from Greece, Iran, Egypt, Sudan, and Nigeria.

Dr. Robert B. Tesh spent 4 months studying the epidemiology of sandfly fever in Iran, as a collaborator funded by the School of Public Health, University of Teheran. The studies involved three geographic areas and were used to train Iran workers in epidemiologic techniques for sandfly-borne diseases, which are important public health problems in the Middle East. Many human, animal, and insect specimens were collected and transported to the Pacific Research Section for laboratory investigations.

Clinical Research

During July and August 1974 Dr. Sheldon M. Wolff, Clinical Director, NIAID, spent several weeks in Brazil where he has gone each summer for the past 3 years. During these visits he lectures to students and faculties, sees patients, makes rounds, and meets with individual scientists to review work and offer advice and ideas. Out of these visits has grown a very close relationship between several of the senior faculty at the Federal University of Rio de Janeiro and the Clinical Director. For example, two senior scientists from the Institute of Biophysics in Rio have spent time working, and one is now in training in LCI, NIAID. The Clinical Director, NIAID, has already accepted invitations to return to Brazil next summer to lecture in Sao Paulo and Rio de Janeiro.

The Clinical Director, NIAID, also spent time in July 1974 and again in June 1975 with collaborators at the Pasteur Institute in Paris, France. These investigators have prepared materials that appear to have properties of inducing nonspecific resistance to infection, and this work has resulted in a paper recently submitted for publication. Plans are under way to eventually evaluate these components here at NIH in human beings.

In June 1975 the Clinical Director, NIAID, presented an invited lecture at one of the major symposia at the International Congress of Nephrology in Florence, Italy. Approximately 1,500-2,000 people from all over the world attended this symposium.

In August 1974 the Head, Biologic Structure Section, LCI, NIAID, visited a number of laboratories in South Africa where he presented lectures and discussed research with senior scientists from the University of the Witwatersrand and South African Society of Pathology (where he taught a course in immunology), Johannesburg, South Africa.

Dr. Charles Kirkpatrick, Head, Clinical Allergy and Hypersensitivity Section, LCI, NIAID, visited in March 1975 the Rheumatic Fever Project in Cairo, Egypt, as a consultant. This is a collaborative project of the Center for Disease Control, DHEW, and the Ministry of Health of Egypt.

Scientific Communications

The NIAID is conducting two experiments for the development of new and improved methods for informal communications between research investigators. These involved a rapid and frequent distribution of short, informal, written communications, and the use of a communication satellite. Both experiments include scientists from many countries and thus are international in operation.

The scientific memoranda contain short, informal progress reports on current research, scientific comments, and any other informal communication pertinent to the research subject covered. Communications are photoreduced and reproduced, without editorial attention, and distributed to the participating scientists monthly or quarterly. Scientists from 47 countries, plus the United States, participate in this project. Separate scientific memoranda exist for interferon, hepatitis, leprosy, hypersensitivity disease, sexually transmitted disease, transfer factor, and nucleic acid recombinants.

The satellite experiment uses the NASA ATS-1 satellite maintained in geosynchronous orbit approximately 23,000 miles above the equator in the middle of the Pacific Ocean. The satellite coverage area includes the whole Pacific Ocean and as far east as Bethesda, Md. Anyone in the coverage area, equipped with relatively small and inexpensive FM radio transceivers with proper frequencies, can communicate directly via the satellite. The NIAID project is purposed in determining the usefulness of this method of informal communication to biomedical research investigators. The project has involved scientists on field trips or in their laboratories in many of the countries and island areas of the Pacific.

Geographic Medicine Branch Program

This Branch of NIAID manages three international programs: the U.S.-Japan Cooperative Medical Science, the International Centers for Medical Research, and the Cholera Research Laboratory in Dacca, Bangladesh.

U.S.-Japan Cooperative Medical Science Program

The U.S.-Japan Cooperative Medical Science program was initiated in January 1965 as the result of a meeting between the Prime Minister of Japan and the President of the United States. The two heads of state agreed to undertake a greatly expanded, joint cooperative research effort in biomedical sciences to improve the health of the people of Asia. The disease categories considered to be of particular importance included cholera, leprosy, malnutrition, the parasitic diseases schistosomiasis and filariasis, tuberculosis, and the viral diseases rabies, dengue hemorrhagic fever, and other selected arboviruses. In 1972 environmental diseases was added as a program interest.

The U.S.-Japan Cooperative Medical Science program operates within a bilateral government framework. Nevertheless, it may involve scientists and facilities in third countries and/or collaboration with international or other organizations. The relevant regions in Asia, although not specifically defined, are generally understood to include the Republic of Korea on the north, India and Pakistan to the west, and other adjacent nations in the broad Pacific basin.

The United States and Japan each support the cost of their own scientific projects and meetings.

1. Cholera

The cholera program has completed a toxoid field trial in some 92,000 persons in the cholera endemic area of Bangladesh. The fall cholera epidemic was unusually severe this past year and provided a most rigorous test of the protective effect of antitoxic immunity to El Tor cholera infection. The conclusion from the field trial of two injections of cholera toxoid (100 mg each) is that protection from antitoxic immunity was transient with no improvement over licensed cholera vaccine. However, this toxoid produced a higher level of protection in the children under 14 years of age than in adults. This finding was unlike earlier field trials with cell vaccines that always gave better protection in the adults and lower protection in children. The level of somatic antigen in the toxoid did not stimulate vibriocidal antibody production in the native population. This confirms the high degree of purity of this toxoid. Work now centers on how to enhance the limited protection seen in the first field trial of a cholera toxoid.

Important observations have been made on the effect of local immunization on resistance. Most significant is that if the dog model was primed with one parenteral injection of toxoid, followed in 1 month by a series of oral doses, there was prolonged protection against cholera challenge. Serum antitoxin levels, however, were notably low. These findings have been confirmed in rats. A similar dose schedule in rats called forth the maximum number of specific antitoxic plasma cells in the lamina propria of the small bowel. Local response required local stimulus, and it was shown that lymphocytes derived from gut-associated lymphoid tissue, such as Peyer's patches, passed through the thoracic duct circulation and returned to the small bowel in the absence of local antigen. This information on local immunity underlines the importance of further studies on the local immune mechanisms.

A chemically induced nontoxinogenic mutant of a highlibrio toxinogenic strain of V cholerae has been fed to volunteers and found to multiply in the gut without producing disease. These volunteers were resistant to challenge with live virulent organisms. The mechanism of resistant is assumed to be antibacterial and the method may hold some promise for a future, live oral vaccine.

Detailed studies on the structure of the cholera enterotoxin molecule has indicated that there were two subunits, designated A and B. Subunit A, the adenylate cyclase-activating component of the enterotoxin molecule, is composed of two chains designated A1 and A2 linked by disulfide bonds. Amino acid sequencing studies have been started in several laboratories.

The U.S. and Japanese cholera panels have catalyzed a cooperative venture between the two countries to standardize the characterization of noncholera vibrios. Two laboratories in each country are involved. The plan is to share type cultures from each country's collection and compare biochemical and serological results with the idea of arriving at a mutually agreeable classification system. The United States has sent 86 type cultures to Japan, and the Japanese have sent 38 type cultures from their collection. The four laboratories are busily engaged in applying their testing schemes to these new cultures. Early results indicate that 31 of the Japanese cultures may be similar to U.S. type cultures.

Studies on the incidence of diarrhea caused by enterotoxin producing E coli are progressing well. The first 40 cases of diarrhea studied in a pediatric hospital in Brazil indicates as many as 50% of the children had lactose fermenting organisms that produced the cholera-like, heat-

labile toxin as the only fecal pathogens. So far, very few E. coli have been found that produce only heat-stable toxin. Thus, the importance of strains that produce only heat-stable toxin in human disease remains unknown. The role of enterotoxigenic E. coli should come into better focus as more cases are added to the study. Material from these E. coli studies is also being examined for the rheovirus-like agent associated with some infantile diarrheas.

Considerable progress has been made on isolating and characterizing a low-molecular-weight, heat-labile toxin from E. coli. The material has been extracted from the culture and reduced to near electrophoretic homogeneity by chromatographic techniques. It is active biologically at the nanogram level and shows strong cross reactions with antisera produced by purified cholera toxin. Attempts are under way to achieve higher yields of this material.

2. Environmental Mutagenesis/Carcinogenesis

Stimulation of the development of better methodology to screen chemicals before they are released into the environment, as well as to provide a thorough evaluation of chemicals already present in the environment, is one of the primary activity areas of this panel. Exploratory experiments on various classes of chemicals (drugs, food additives, pesticides, cosmetics, industrial compounds, etc.) have already shown that there are numerous examples of agents that have genetic activity in experimental organisms. The main question is to determine their effect on man. In addition, recent studies have shown that there is some correlation between carcinogenic and mutagenic activity and evidence of mutagenic activity in experimental organisms may mean that a chemical not only presents a genetic hazard to man but a carcinogenic hazard as well.

To ensure the effectiveness of any screening program established, new approaches will have to be developed for population monitoring and epidemiology. Better tests are needed to evaluate the effects of accidental or deliberate exposure to mutagenic agents on somatic cells and germ cells in man. Exposure of somatic cells may induce damage that will make an individual more susceptible to the development of various types of cancer; exposure of germ cells may induce damage that will be transmitted to future generations.

One of the major deficiencies in testing is the lack of assays that can be made on somatic and germ cells of man for the production of gene mutations. In one project an attempt is being made to develop an assay for gene mutations induced in germ cells. By using loci that produce proteins that can be studied with starch gel electro-

phoresis, it is possible to look for "electromorphs" (altered proteins with different electrophoretic mobility) or "amorphs" (changes that result in complete loss) at specific loci. The program of research seeks to identify additional loci at which such analyses can be made so that numerous tests can be performed on progeny of the same treated animal.

In another project the research is directed toward the development of an assay in mice that will permit assay of a random sample of loci over the entire genome. Development of mouse strains containing large numbers of inversions will permit assay of the recessive lethal mutations occurring in these regions.

The development of better methods for detection of point mutations in somatic cells is the objective of another project that utilizes blood samples to determine the frequency of variant red blood cells. Normally, only a very low percentage of erythrocytes contain fetal hemoglobin. An assay is being developed with selective antisera to determine the frequencies of such variants quantitatively.

The development of assays for gene mutations at specific loci is under way in another project utilizing human fibroblasts in culture. This system utilizes the hypoxanthine-guanine phosphoribosyltransferase (HGPRT) locus as well as the azaguanine phosphoribosyltransferase (AGPRT) locus. Present data clearly indicate that drug-resistant mutants result from genetic changes at these two loci that result in structurally modified enzymes. The spontaneous frequency of variants at each locus has been determined in various individuals as has the induced frequencies obtained after mutagenic treatment.

The better detection of the genetic activity of airborn environmental pollutants is the objective of an additional project with the wildflower Tradescantia. By using a strain heterozygous for flower petal color, it is possible to observe pink and colorless sectors in normally blue flower petals and stamen hairs. The assay system is a very sensitive detector of the mutagenic activity of radiation, and exploratory experiments are in progress to determine its sensitivity to various chemicals including known chemical mutagens.

The collaborative efforts of the United States in this program are provided through the National Institute of Environmental Health Sciences and the National Institute of Allergy and Infectious Diseases.

3. Leprosy

The three areas of leprosy research that continue to receive special emphasis include immunology, chemotherapy, and cultivation and transmission in animal models.

Excellent progress has been made in preparing transfer factor (T.F.) to be used in a controlled clinic trial to evaluate the immunotherapeutic response of this agent in the treatment of lepromatous leprosy. Efficacy of T.F. will be determined by in vitro laboratory studies that measure cellular mediated immunity, as well as by clinical assessment to evaluate any improvement of localized lesions. It is anticipated that at least 2 years of continuous observation will be required to draw conclusive results on the efficacy of this form of immunotherapy.

The fourth annual surveillance of post-treatment of leprosy patients among the Pingelapese population was completed in February 1975. At present, the investigators have concluded that eradication of leprosy in an endemic population by use of DADDS for preventive treatment cannot be totally effective without simultaneous and continous drug control of all bacilliferous cases. Studies will continue in FY 1976 to determine if mass treatment with DADDS is associated with the emergence of sulfone-resistant infections.

Studies on the in vitro cultivation of Mycobacterium lepraemurium were initiated by a research contract during the past year. Preliminary work has demonstrated that fetal calf serum is superior to goat or bovine sera as a supplement to Nakamura's basal medium. A thorough evaluation of the efficiency of different sera is in process. Other factors, such as microaerophilia and levels of aerobiasis, are under investigation to determine methods and techniques to enhance in vitro cultivation of M. lepraemurium. The nine-banded armadillo continues to be an outstanding animal model for the in vivo cultivation of large quantities of M. leprae. Steps have been taken to establish and support a continuous colony of armadillos infected with M. leprae. This potential source of M. leprae will provide a strong stimulus to future studies to ascertain the immunochemistry and antigenic properties of the various purified components of the organism.

4. Parasitic Diseases

A major breakthrough in the development of S mansoni culture systems for studying the growth and development of schistosome parasites was achieved when one of our contractors established a cell line from embryos of the snail host, Biomphalaria glabrata. Suitable media and

culturing techniques have been described in detail and are being utilized by investigators in studying larval stages of S. mansoni in vitro.

Studies of the possibility of the biological control of schistosomiasis have shown that Biomphalaria glabrata snails have the potential to develop acquired resistance to trematode infections. This finding will make possible the study of the basic principles of snail immunity.

A major granuloma-inducing antigen has been isolated to a single band on polyacrylamide gel electrophoresis. A radioimmune assay has been developed using this antigen, and the development of antibody against it correlates with the waning of granulomatous hypersensitivity.

A joint meeting with the Japanese panel was held in August 1974 in Nagasaki, Japan, and a workshop on "Animal Models of Filariasis" was held in Bethesda, Maryland, in April 1975. At this workshop it was reported that four species of monkeys had been inoculated with a Tongan subperiodic strain of Wuchereria bancrofti resulting in developing worms. This was the first definitive evidence that W. bancrofti, thought to be an exclusively human parasite, will mature in monkey hosts. This finding should expand the scope of filariasis research to include a wide variety of studies on this important human disease.

Ultrastructural studies of the development of Brugia Malayi larvae in the mosquito vector's flight muscles have demonstrated a specialized surface that is suggestive of absorptive function during a phase of rapid growth and development. This is the first demonstration of such a function in filarial larvae, and it is hoped that supplementary biochemical studies will follow.

5. Tuberculosis

The research sponsored this past year by the tuberculosis program again focused on the immunologic aspects of tuberculosis. The monkey model for studying aerosol BDG vaccination with aerosol challenge continues to be investigated. Previously, it was shown that the route of administration of BCG vaccine significantly affects the degree of protection against aerosol challenge with virulent tubercle bacilli. Inhalation of the vaccine or administration by the intravenous route confers a higher degree of resistance to challenge than does intracutaneous administration of vaccine. The protection afforded by aerosolized vaccine was also found to be related to the total dose of viable units administered. The highest dose tested, 105 (vu) was the most effective. As an adjunct to this study, it was found that previously sensitized guinea

pigs did not display clinical signs of pulmonary distress after exposure to aerosolized BCG; however, there was an indication of slight, but statistically significant, increase in total airway resistance following exposure.

A study is now under way to determine the duration of protection afforded by aerosolized BCG as opposed to intracutaneously administered BCG. Deaths in animals challenged 8 and 28 weeks following vaccination are less than in the control group. Less pulmonary infiltrate is seen in radiographs of those animals receiving the intracutaneous vaccine. As a follow-up to the guinea pig pilot study with BCG-sensitized lungs, a more comprehensive study with monkeys has recently been initiated.

The relationship of delayed-type hypersensitivity to one or more microbial antigens in the immunized host and the expression of cell-mediated immunity (CMI) against a virulent challenge organism have been clarified. It has been established that a sensitizing preparation must be used if an effective antibacterial resistance is to be developed. Large doses of living bacilli may induce an effective CMI in the apparent absence of peripheral DTH but transfer studies showed that the anergic animals still contained sensitized lymphocytes capable of transferring tuberculin sensitivity to normal recipients.

Migration inhibitory factor (MIF) and a new type of interferon (type II) are released into the circulation after mice have been sensitized intravenously with viable BCG and challenged later with old tuberculin. In this *in vivo* production of mediators the activity of MIF was at least 100-fold greater than the MIF induced *in vitro*. Two components of BCG, the protein PPD and the lipid P3 necessary for the production of MIF, were also necessary for the induction of resistance to a virulent aerosol challenge. In preliminary studies, the production of MIF *in vivo* in mice seems to be associated with both B and T lymphocytes. Other studies involving the basic immune mechanisms of the mycobacterioses continue.

This year a task group convened at the National Institutes of Health to discuss the role of soluble mediators of cellular immunity in tuberculosis. These substances have been shown to be of immense biological and clinical importance and are the subject of widespread investigation. A general overview of the problem area was discussed, those areas where the U.S.-Japan program could provide support were identified, and a list of priorities to facilitate orderly progress of the research were developed.

Highly characterized and standardized mycobacterial materials continued to be available to qualified scientists working in tuberculosis and related areas.

6. Viral Diseases

Studies have established that protection from virulent intracerebral challenge with rabies virus is directly dependent on the level of specific neutralizing or lytic antibody present at the time of challenge. Inactivation of rabies virus by beta-propiolactone was evaluated by the rabies fluorescent focus inhibition test (RFFIT) and was shown to leave no detectable residual infective virus. The RFFIT was found to be more reproducible than the mouse neutralization test, requires less time for completion, and is less expensive. A major rabies glycoprotein has been extracted by exposure to alkaline EDTA. Physical chemical procedures attest to the purity of the glycoprotein preparation. This protein consists of a single polypeptide chain with a molecular weight of 70,000 daltons. Its biological activity was demonstrated by immunization of hamsters, rabbits, and mice.

Recent studies on skin biopsy material from dengue patients indicate that skin rashes in these cases are likely to be immunopathologic in nature. It also has been shown that in acute stages of dengue hemorrhagic fever and dengue shock syndrome, B lymphocytes and certain dengue antigen antibody combinations form immune complexes on cell surfaces. In studies of the epidemiology of dengue virus in the jungles of Malaysia, it has been shown that dengue is a zoonosis involving wild monkeys in the primary rain forest. Recent emphasis has been on attempts to identify the mosquito species that serves as the important jungle vector. Evidence has been obtained showing that enzootic dengue, involving at least three of the four known virus types, occurs in the high canopy of isolated primary rain forest and that Aedes niveus mosquitoes are most likely the jungle vectors. Other vector studies have uncovered a marked variation in susceptibility of dengue viruses and the stability of this character from generation to generation. This could be of great importance in controlling epidemic dengue. Results suggest that it might be possible to achieve disease control in an area by replacing a susceptible vector population with a more refractory strain of the same species.

7. Malnutrition

Although malnutrition is one of the categories included under the U.S.-Japan program, this area is partially administered by NIAMDD and will be included as part of its report.

International Centers for Medical Research (ICMR) Program

In response to the expressed desire of the Congress (PL 86-610), a program for the International Centers for Medical Research was established in 1960 by the National Institutes of Health "to advance the status of the health sciences in the United States and thereby the health of the American people" by expanding collaborative research between U.S. universities and selected foreign institutions and investigators. Since 1968, this program has been administered by the National Institutes of Allergy and Infectious Diseases.

The four grants funded under this program are awarded for 5 years with continued support contingent upon program review at the end of each year of operation. One of the most important features of this program is that of long-term support, as contrasted with the transiency that has characterized a number of other international projects. This is a necessary ingredient for the full development of university careers in science in order to effectively utilize the international medical experience of individual scientists. This program provides opportunities for established and highly competent investigators to realize valuable research opportunities abroad without losing their university affiliations and faculty appointments. The long-term support of the ICMR does not represent a form of foreign aid since the primary objective is a collaborative effort in biomedical research of specific relevance to the health of the American people and to the U.S. scientific community. The four current ICMR grants were renewed for an additional 5 years beginning FY 1975.

1. Purpose and Scope

The ICMR program has as its principal objective the provision of high quality research and scientific opportunities for Americans in the broad fields of geographic medicine and in response to the special opportunities existing with each ICMR framework. The length of the research period overseas is a discretionary concern of the ICMR program director and is obviously determined by both the interests of the prospective investigator and the specific opportunities available within the given ICMR unit. Consistently, the emphasis is upon the quality rather than the quantity or duration of the research programs.

The aggregate ICMR units are serving increasingly as a national resource for utilization by senior, as well as less experienced, scientists to create a comparatively modest pool of investigators with a sustained career interest in international or geographic biomedical research. In this regard, the ICMR program directors are encouraged to establish a selective, interdisciplinary scientific program. Their activities encourage and accommodate a number of parent university departments other than the department that primarily sponsors the ICMR operation. Particular advantage is taken of special strengths within the overall parent university, including opportunities in health-related fields outside the classical confines of tropical medicine. As far as is possible, the ICMR core grant is used for research support at the offshore ICMR site rather than at the parent domestic university. In this regard, it is accepted that some preparation preliminary to an overseas assignment is necessary and as many items of equipment and supplies as feasible are purchased in the United States.

Discussion of the four institutions participating in the ICMR program at present and their respective areas of research interests follows:

1. Johns Hopkins University (Baltimore, Md.)
   Program Director: Dr. Frederik B. Bang

Several years ago, Johns Hopkins University transferred its operations from Calcutta to Dacca, Bangladesh, to take advantage of the facilities at the Cholera Research Laboratory and to initiate a series of studies on Bangladesh disease problems that had been previously studied by the Hopkins group in India. Program emphasis continues to be directed toward the epidemiology and management of human diseases of large populations and the ecology and behavior of animals living in close association with man. Research on cholera and other diarrheal diseases constitutes the core of the program and includes studies of the effect of zirconium oxychloride on fluid loss, oral sucrose therapy, collection of toxinogenic strains of Eschlerichia coli, studies of leukemoid reactions and hemolytic anemia in shigellosis, determination of T and B cell response in Shigella infection, and a study of the association between malnutrition and diarrheal diseases. Related studies are directed at the effect of protein calorie malnutrition in immunological competence. Three programs were conducted during the past year on parasitic diseases: epidemiology of endemic filariasis; epidemiology of echinococcosis; and a study of local malaria vectors.

Ecological studies have been initiated to determine the contribution of rodents and insects to crop and store grain loss, to correlate the rate of fish growth with food sources and water quality, and to determine how to maximize the benefits of dung beetles, distribution of feces in soil, and maintenance of soil porosity.

2. University of Maryland (Baltimore, Md.)
Program Director: Dr. David Clyde

The University of Maryland, with the participation of its School of Medicine and collaborating with the Institute of Hygiene, Lahore, has undertaken a varied research program in West Pakistan. This program during the past year has continued to be based on studies of the genetics of important insect vectors of virus and parasitic diseases. The objective is production of strains with lessened vector ability. Associated with the investigation of the genetics of Anopheles stephensi, a principal carrier of malaria in central and western Asia, has been an examination of the resistance of local strains of this mosquito to insecticides, an increasingly serious problem for the malaria eradication campaigns of Pakistan and neighboring countries. Genetic manipulation of Culex tritaeniorhynchus, important in the transmission of Japanese B encephalitis, West Nile, and Chikungunya viruses and ranging from East Asia to West Africa, is yielding results that will permit early field application on a limited scale.

3. University of California (San Francisco, Calif.)
Program Director: Dr. Albert Rudnick

The University of California, with the participation of the Hooper Foundation, the School of Public Health, and the Medical School, is collaborating with the Institute for Medical Research, Kuala Lumpur, Malaysia and the University of Malaya. This international center continues to place strong emphasis on infectious diseases transmitted from animals to man. Because of the long-standing research interest and experience in studying the fundamental problems of human ecology at the University of California, a collaborative program has been developed embracing medical zoology, microbiology, and parasitology. The scope of this collaborative endeavor has now been expanded to include related sociocultural research and medical genetics.

Long-term research projects in Malaysia and California are based on three general laboratory programs: the Arbovirus Research Unit; the Parasitology Laboratory; and the Medical Anthropology and Rural Health Research project.

The arbovirus research is focused on the epidemiology and ecology of dengue virus and the relationship of this

virus to mosquito-borne hemorrhagic fever. A jungle reservoir (monkey) has recently been demonstrated for dengue. The parasitologic research is based on studies of trematode ecology and interactions of various parasites in the snail host and the ecology of Malayan pentastomes or tongue worms. The snail trematode antagonism studies are directed toward the biologic control of schistosomiasis, and this ICMR represents a leading world resource for this important field research.

Abundance, distribution, life cycle, and ectoparasites of rodents closely associated with man have also been studied. Work on the possible role of the Indian fruit bat as a reservoir of human viral infections has been completed. Other field studies include the investigation of bacteria and viruses pathogenic for man in monkey populations. Sociocultural studies concerned with Malayan attitudes toward health and nutrition and the influence of native and western practitioners of medicine on these attitudes have been undertaken by a number of variously trained, medically oriented social scientists.

4. Tulane University (New Orleans, Louisiana)
Program Director: Dr. Paul C. Beaver

Tulane University, with the participation of the Department of Tropical Medicine and Public Health, other departments of the Medical School, and the Department of Anthropology and Sociology, has been collaborating with the Universidad del Valle, Cali, Colombia. The research work falls into three general areas: Nutrition and metabolic diseases; Infectious diseases; and Behavioral science.

Parasitological research includes classic life cycle approaches to the epidemiology of paragonimiasis, trypanosomiasis, and animal malaria, taxonomic studies of Culicoides and tabanids, an overall study of the parasites of bats, and a broad program of filariasis research with emphasis on onchocerciasis. Two principal virological studies have just been initiated in cytomegalovirus and on patients with Guillain-Barre disease. The objectives of the mycology program are centered primarily on the systemic mycoses, especially paracoccidioidomycosis, the most important deep mycotic infection in Colombia. These studies encompass both epidemiology and immunology.

The nutrition program at the ICMR in Cali encompasses a variety of research activities including studies of the malabsorption syndrome in protein calorie malnutrition, enterobacteriology of protein calorie malnutrition, thyroid function studies in adult malnutrition, evaluation of protein quality for children, and a study of the nutrition and feeding habits of a community. A related study has been concerned with immune responsiveness in normal and mal-

nourished infants.

Currently, the behavioral science program is emphasizing shorter-term, small projects in five areas: social psychiatry and behavioral disorders; evaluative research and health systems; medical anthropology; social demography; and health service utilization.

Cholera Research Laboratory, Dacca, Bangladesh

The Cholera Research Laboratory (CRL), Dacca, Bangladesh, continued operations during fiscal year 1975, financed principally by the Agency for International Development (AID). Through a participating agency agreement, the National Institute of Allergy and Infectious Diseases (NIAID) provided both the administrative and scientific support to the CRL. In addition to this staff support by NIAID, the Center for Disease Control deputes two EIS officers to Dacca; the Government of Bangladesh provides space in the Institute of Public Health and the Rural Health Center in Matlab Thana, plus utilities and a cash contribution. The governments of Australia and the United Kingdom have also contributed funds, equipment, and services to the CRL.

The research program at CRL centers around diarrheal research involving field studies and clinical research. The past year demonstrated the capabilities of the CRL to handle a large field trial involving over 90,000 persons in a test of a cholera toxoid. The number of cases of cholera during the fall epidemic provided an excellent test of antitoxic immunity against cholera. The protection was of a low level and transient with no improvement over licensed cholera vaccine. Of particular interest was the higher level of protection in the children under 14 years of age. This was directly opposite to early cholera vaccine trials that demonstrated the lowest protection in children and highest in adults. Methods of improving this protection are being sought. The field trial population will remain under surveillance to measure the effect of the toxoid on the second cholera season.

The development of the oral electrolyte solution for treatment of dehydration has received worldwide acceptance. However, the difficulty of finding glucose for the formula is a problem in some areas of the world. Further testing at CRL has found that contrary to earlier data, sucrose appears to be as effective in aiding electrolyte absorption as glucose. A new formula including sucrose is being tested in diarrhea patients.

The studies measuring the effect of a low pH and fluid secretion in the small bowel have revealed the rapid loss of the villous tips lining the small bowel. It is assumed that the sudden reduction in fluid loss is due to removal of these toxin-activated cells that are hypersecreting. Animal studies are continuing, and a clinical protocol has been submitted for approval. The value and practicality of this treatment have not been firmly established yet.

In a study of 50 patients with diarrhea of unknown etiology, nearly one third were found to have toxigenic Escherichia coli present in the bowel. In addition to the heat-labile toxin found in other toxigenic E. coli studies, there were two strains of E. coli producing only the heat-stable toxin. This is the first recognition in Bangladesh of an E. coli strain that produces only the heat-stable toxin. Its relation to disease production in man is not yet known.

Shigellosis continues as a major problem in Bangladesh. In addition to the leukomoid reaction in severe cases, one third to one half these cases also develop acute hemolytic anemia associated with erythrocyte fragmentation. Blood transfusions will correct the anemia, but the pathogenesis remains unknown. It was also noted that shigella infection causes a depression of the percentage of T cell rosette-forming lymphocytes, while B cells remain at normal levels. In addition, there is a large population of cells not countable as T or B cells. These "nil" cells amounted to 10 to 60 percent of the total lymphocytes, compared with 3 percent in normal individuals. It is not certain whether these "nil" cells are another type of lymphocyte, immature lymphocytes, or a new undescribed cell.

Over half of all patients coming to CRL hospitals are seriously malnourished. The CRL is taking advantage of this fact by studying the effect of malnutrition on diarrheas. The malnourished patients, on the average, purged longer than comparable patients in better nutritional status. There was no noticeable effect on volume/unit of time. This extended period of diarrhea may be due to the prolonged life of the mucosal cells activated by cholera toxin in patients with malnutrition. Another study was designed to relate malnutrition and infection through cell-mediated immunity. The children below the 50th percentile of Matlab standards for weight and height have twice the incidence of allergy as children above the 50th percentile. This suggests that cell-mediated immunity status may be an important independent determinant of diarrhea in addition to nutritional status.

The demographic data available from the 250,000 persons in the surveillance area are being recognized as a unique data base unavailable in any other developing country. With the continuing census information, it is possible to do rate studies in this population that cannot be done in other developing countries due to the lack of a definitive denominator. A 3 year study on the effect of birth control measures is under way.

U.S.-U.S.S.R. Cooperative Science Agreement

A memorandum of scientific cooperation between Soviet and U.S. rheumatologists was signed May 22, 1975, at the National Institutes of Health. Dr. Ronald W. Lamont-Havers, then Acting Director, NIH, and a specialist in the rheumatic diseases, and Professor V. A. Nassonova, Director, Institute of Rheumatism, Moscow, signed an agreement to formalize the continued exchange of scientific data and personnel in the field of arthritic diseases between these two countries.

This agreement, the third in a series of cooperative memoranda signed last year in Moscow, culminated 5 days of intense discussion on two major areas: evaluation of different methods of drug treatment for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), the latter an autoimmune disorder of the connective tissue that affects the structure and function of skin, joints, and internal organs; and microbial and immunologic studies of RA and SLE.

Through a series of bilateral exchanges of scientific personnel, the program will emphasize studies of antiviral, humoral, and cellular immunity in SLE and RA and the exchange of information in immunologic and other research methods. In addition to these and other planned activities, reprints and lectures pertinent to problem areas will continue to be exchanged. A symposium to evaluate preliminary results and plan future projects is scheduled for Moscow, late summer 1976.

The cooperative study of the arthritic diseases is the fourth major collaborative undertaking in the health sciences between the United States and the U.S.S.R. Earlier agreements, including those in vascular diseases, cancer, and environmental health, were begun under the initial 1972 agreement on cooperation in the field of medical science and public health.

The accord was formulated by the Soviet delegation, including Professor Nassonova and colleagues Drs. A. I. Speransky and M. M. Ivanova, and U.S. scientists headed by Drs. Lamont-Havers, William Batchelor, and Alfred Steinberg, NIAMDD.

Nutrition Studies in South America

In the area of malnutrition and its possible effect on mental development, Dr. Adolpho Chavez and associates (Mexico City) have documented the nutritional, sociologic, psychologic, and environmental factors surrounding their subjects to determine their influence on physical and mental development. At the end of 3 years, the investigators have been able to demonstrate that mothers given food supplements produce more milk and thus maintain a nutritionally adequate plateau for at least 24 weeks after delivery. Significantly, the physical activity of children who received food supplements was higher and became increasingly elevated after the first year, reaching a level six times higher than that of the unsupplemented group by 2 years of age. Furthermore, the unsupplemented group showed a 20-week retardation in neurologic development in the lower extremities and had lower scores in language ability. Both groups suffered a similar number of infections, but the total number of days of illness and the severity of the infections were significantly higher in the unsupplemented group.

In other studies of malnutrition and infection, Dr. Leonardo Mata of the Institute of Nutrition of Central America and Panama has documented the high incidence of bacterial and viral infections and infectious diseases of all types, including malnutrition, in children living under conditions characteristic of developing countries. Dr. Mata's graphic demonstration of the association between frequency of infections in preschoolers and their impaired physical growth and development led him to conclude that weight at birth is the best predictor of child survival. Only 2 of 81 infants weighing at least 2,750 grams at birth died within the first 6 months; no deaths were recorded among babies weighing 3,000 or more grams. Survival rates decreased sharply with lower birth weights.

Because these deaths largely resulted from diarrheal or respiratory disease, they were attributed in the main to decreased resistance to infection. There was evidence that the effect on the fetus of the mother's malnutrition during pregnancy was mediated through a higher frequency of intrauterine infections, as judged by levels of immunoglobulins in blood samples taken from the infants at birth.

These observations have awakened widespread interest in the relationship between maternal nutrition and infant birth weight with subsequent morbidity, mortality, and physical growth, as influenced by the interactions of malnutrition with infection in mother and child.

U.S.-Japan Cooperative Medical Science Program

Specific research projects, carried out abroad among populations with nutritional deficiency diseases, are designed to find solutions to complex malnutrition problems. These projects are largely funded through the U.S.-Japan Cooperative Medical Sciences program and through the Public Law 480 foreign currency program using U.S.-owned local currencies derived from the sale of surplus agricultural commodities in developing countries. Only half the earth's population maintains an adequate diet, indicating a critical need for research to find technologic ways and means to transform marginal nutrition and overt nutrition deficiency to adequacy.

Traditionally, the National Institute of Arthritis, Metabolism, and Digestive Diseases has conducted nutrition research in developing countries because of the availability of large population groups afflicted with specific nutritional deficiences that can be readily studied. The results from such research are twofold: It may stimulate emergence to self-sufficiency from mere subsistence in Southeast Asian countries, as well as add to knowledge concerning normal nutrition and nutritional requirements that will benefit the U.S. population.

The startling realization that malnutrition can, in fact, exist within our own population lends an element of expediency to nutrition research. By providing scientific know-how for effective utilization of economical, indigenous protein sources, these programs also discourage dependency of developing countries on the United States for provision of expensive protein-rich foods and enable them to make inroads against endemic protein malnutrition.

The mission of the malnutrition segment of NIH's U.S.-Japan Cooperative Medical Sciences program is to support both basic and applied research aimed at practical solutions to nutrition-related problems in the countries of South East Asia and other nations in the Pacific area.

The substantial grant and contract program has already brought about significant findings that will help to improve the protein level of rice, the principal food of 60 percent of mankind. Ordinary commercial rice lacks sufficient protein for normal growth and development of children maintained on a predominantly rice diet; in addition, it does not protect the adult population from serious protein undernutrition.

Research identified approximately 100 rare rice varieties that contain from 13 to 17 percent protein in contrast to the conventional level of 7 1/2 percent in

currently available commercial rice varieties. A vigorous plant breeding program has been started with the aim to develop a variety of high-protein rice that has all the necessary additional qualities (such as disease resistance, high yield per acre, identical taste and mouth-feel as conventional rice) that would make possible and commercially feasible large-scale planting and distribution of high-protein rice.

In the future, however, because of a change in the protocols of the U.S.-Japan program, the agricultural portion will no longer be supported by NIH funds. While the human nutrition aspects of this project will continue under the auspices of NIAMDD, the International Rice Research Institute in Los Banos, Philippines, has assumed responsibility for agricultural experimentation.

Studies of the distribution, importance, and methods of control or elimination of natural toxic substances in legumes and other plant foods focused primarily on the distribution of mycotoxin in the food supply of Asian countries and its relation to human disease. The principal work, supported by a contract with Drs. Gerald Wogan and Ronald Shank of the Massachusetts Institute of Technology, has now been concluded. Their studies resulted in the publication of 15 scientific papers documenting the widespread occurence of aflatoxin and other mold toxins in Asian foods and their probable association with liver damage in those who habitually consume foods contaminated with such toxins.

The investment in a large nutritional research center in Chiang Mai, Thailand, has yielded a significant amount of data in two priority areas of the U.S.-Japan program-- nutritional anemia and interactions of malnutrition and infections. In studies by center personnel, almost 80 percent of the more than 1,500 children attending the hospital's outpatient department were found to be iron deficient and responded completely to iron therapy. In a companion study, 3,230 pregnant women were surveyed for hematologic status: 70 percent were iron deficient; 20 percent, folic acid deficient; and 13 percent had combined deficiencies. Of particular interest was one case of pernicious (Addisonian) anemia discovered during the study-- the first reported in a Thai.

The latest study reported from Chiang Mai explored the role of varying amounts of protein and calories on the hematologic responsiveness of children with protein-calorie malnutrition (PCM). In this investigation, the addition of protein and calories elicited a therapeutic response, with protein recording the greater effect. Part of this action is thought to be related to the responsiveness of erythropoietin (a glycoprotein considered

to be the humoral plasma factor that stimulates red cell production in the bone marrow) to protein feeding.

Bladder Stone Disease in Thailand

Bladder stone disease is one of the most serious health problems in northern Thailand, occurring primarily among village children 5 years of age and under. Research by NIAMDD grantees Drs. Aree Valyasevi and Sakorn Dhanamitta indicates that oxalcrystalluria (excessive amounts of crystalline oxalic acid salts in the urine) was commonly found in urine samples of villagers, but only rarely in specimens of city dwellers. Moreover, calcium oxalate was shown to be one of the main constituents of the urinary stones.

A dietary survey showed that the villagers daily consumed several kinds of local vegetables and leaves of forest plants not eaten by the townspeople. Further study revealed that these food items such as tampala and bamboo shoots were high in oxalic acid content, possibly leading to the heavy oxalcrystalluria and crystal clumping, particularly among children.

To counteract this occurrence, the investigators at Ramathibodi Hospital in Bangkok administered oral doses of orthophosphate, which eliminated almost all crystalluria and crystal clumping in the patients studied.

The researchers concluded that in all future studies on the origin of bladder stone disease, external sources of oxalic acid (which heretofore had not received as much attention as the possibility of metabolic abnormalities) should be an important consideration.

NATIONAL INSTITUTE
OF
CHILD HEALTH AND HUMAN DEVELOPMENT

Nutrition

The National Institute of Child Health and Human Development (NICHD) is conducting a series of coordinated studies on nutrition and mental development. The largest of these is a contract-supported study begun in 1964 in cooperation with the Institute of Nutrition of Central America and Panama and the Pan American Health Organization. The data from four small rural villages in Guatemala indicate that consumption of a dietary supplement by undernourished pregnant women may increase birth weight of babies to approximately the birth weight observed in more favored populations. Infant mortality also has been reduced by this supplementation. Preliminary data suggest there may also be some beneficial effects on early behavioral development.

In a smaller grant-supported study under way at the Institute for Mother and Child in Mexico, food supplementation of the mother and infant has greatly increased the level of activity and alertness of the infant. In addition, it has increased the interaction between the mother and her child.

Two other projects are under way in Colombia in cooperation with U.S. universities. The first utilizes regularly available food items to improve the diet of pregnant women or children in urban Bogota. The Colombian Institute of Nutrition specialists and scientists from Harvard University are seeking to determine when the supplementation program should be introduced in order to effect optimal changes in growth, health, and behavior of the offspring. The second Colombian project is under the direction of a research team from Northwestern University and the Universidad del Valle in Cali, Colombia. These studies focus on undernourished preschool children. The data suggest that both nutrition intervention and an educational stimulation program may be necessary to overcome the deleterious effects of early malnutrition.

Still another project is under way through the University of Santiago, Chile. This study is seeking to clarify the complex interrelationships among malnutrition, maternal IQ, and other social variables that influence a child's mental development.

Using money allocated from the U.S.-Japan Cooperative Medical Science program, another NICHD joint project with

the Institute of Nutrition of Central America and Panama, consisted of a 9 year longitudinal study of nutrition, infection, and growth among pregnant and lactating women, infants, and children of a small native village in Guatemala. A monograph summarizing these findings will soon be published.

Another joint NICHD-Institute of Nutrition of Central America and Panama project consists of two concurrent studies on the ecology of infection, malnutrition, and growth of children in two Guatemalan Indian villages. One study seeks to determine whether the antibacterial defenses of the newborn are influenced by maternal nutrition status, birthweight, and general health status of the infant. The second study is assessing the ability of malnourished children to elicit and maintain appropriate humoral antibody response to measles vaccine and natural measles infection. An ongoing project funded by the Office of Nutrition of the Agency of International Development provides nutritional supplementation to the families of one village; a second village serves as a control.

Population Research

The Center for Population Research (CPR) of the NICHD has several important contracts and grants with institutions outside the United States,some of which are described here. As part of its efforts to develop a variety of safe and effective contraceptive methods for both men and women, CPR supports studies at Laval University, Montreal, Quebec, Canada, to synthesize chemical analogs of steroidal antifertility compounds and in an effort to identify the chemical factor in the testicles that regulates spermatogenesis, CPR has contracted with the University of Trondheim, Norway.

Under contract from the CPR the Medical Information Center at the Karolinska Institutet, Stockholm, Sweden, supplements and enhances bibliographic data available through the National Library of Medicine in the biological and medical fields relevant to human reproduction. The Human Reproduction Thesaurus produced by the center includes citations to journal articles, technical reports, monographs, and symposia not previously included.

As part of its program to evaluate the long-term effects of vasectomy, the CPR has contracted with the Netherlands Cancer Institute, Amsterdam, to study human sperm antigens and the development of antibodies in naturally infertile and vasectomized men. A new antigen from human sperm, the "swollen sperm head antigen," has been demonstrated in sera of vasectomized men, and its possible medical significance is being investigated.

To evaluate the effect of oral and other contraceptives on congenital abnormalities and outcome of pregnancy, a research project is being supported with the Hebrew University-Hadassah Medical School in Jerusalem, Israel. This study will measure the effects of contraceptives used prior to and at the time of conception on outcome of pregnancy, especially the incidence of congenital defects and chromosome aberrations.

A contract with the Mario Negri Institute of Pharmacological Research in Milan, Italy, supports a wide range of studies of the effects of currently used contraceptive steroids in laboratory animals. This project is part of a program designed to define better animal models for predicting possible adverse reactions to these agents in women.

In the behavioral sciences, a grantee at the Hebrew University, Jerusalem, Israel, is studying the conditions that affect fertility patterns in Israel among Arab and Jewish populations.

Another project in the behavioral sciences is analyzing census and national longitudinal survey data to determine the relationship between urbanization/migration and fertility in Thailand. The high fertility and low mortality characterizing Thailand place its population among the fastest growing in the world. In analyzing such data this study will add another perspective to the understanding of influences upon fertility behavior.

Remedial Learning

Under a grant from the NICHD, a team of investigators in Israel have developed a highly successful and innovative program that has significantly improved the mental performance and learning skills in adolescent, low-functioning immigrant children from markedly disadvantaged cultural backgrounds. Departing from standardized intelligence tests and question-and-answer methods as an assessment device, the investigator has developed a "learning potential assessment device" in which the tester trains the child to learn principles underlying problems - to make analogies and inferences. Through this dynamic intervention process, the child overcomes deficient ways of functioning and his progress offers diagnostic insights into how much he can be helped.

Once the child's potential has been ascertained, he begins a system of carefully graded exercises (instrumental enrichment) designed to stimulate his curiosity, to enable him to compare different aspects of his environment, and to categorize and think about his behavior. By contrast, teaching techniques in the United States for

children with learning disabilities are concentrated primarily on the learning of skills and transmission of knowledge.

This approach has been widely adopted with remarkable success by the Israeli school system and in special military training units for illiterate and educationally retarded youth. Although data are not yet fully reported, hundreds of disadvantaged youths have successfully completed school and gone on to lead useful, constructive lives. Through a series of seminars, American and Canadian scientists are beginning to apply and test these techniques in their own research facilities and classrooms.

This project is now in its final year of operation and data analysis. The investigator is near completion of a manuscript for book publication (in the United States) in which the theoretical rationale underlying his diagnostic and intervention methods and instrumentation will be elaborated for application in this and other cultures. There is a strong possibility that the techniques developed in this project could have direct relevance to seriously disadvantaged populations in the United States.

Sudden Infant Death Syndrome

The NICHD is supporting three foreign studies of the sudden infant death syndrome (SIDS). An animal model for the study of SIDS is being developed at the Nuffield Institute for Medical Research, University of Oxford, England. The Oxford investigators had previously found that certain liquids, such as water, sugar water, cow's milk, human and artificial milks, would trigger apnea (periods of nonbreathing) in newborn lambs. Under contract with the NICHD, these investigators are studying how the larynx and its nervous control may relate to the arrest of breathing in fetal and newborn lambs and kittens; particularly, what effects do fluids such as water (with and without sugar) and milk have on closure of the upper airway? So far the investigators have found that at a certain stage in development kittens are more vulnerable to the fluid stimulus. They have identified two nerve receptor areas in the upper airway of the kittens that seem to be involved in the fluid-triggered apnea response.

Pursuing a lead that SIDS may result from inadequate lung responses, a grant-supported study at the Hospital for Sick Children in Toronto, Canada, is exploring the hypothesis that some infants' lungs cannot respond to stress on their respiratory system and that this might contribute to the occurrence of SIDS. A Canadian scientist is taking measurements of breathing activity, such as mouth pressure, lung capacity, and frequency of inspiration/expiration in newborn and older infants. Calculations with

these data should produce a method of measuring the elasticity and strength of the respiratory system of the newly born and young infant.

A contract with the University of Toronto, Canada, supports studies to characterize the effects of respiratory tract sensory feedback on the respiratory behavior of adult cats and kittens. A particularly striking observation has been that the activity of only 50 percent of the rhythmically active neurons in the adult could be suppressed by peripheral sensory feedback, while the discharge of all similar cells so far tested in the kitten was suppressed. Differences have also been found in excitory input between the adult and infant animals. These preliminary findings that the suppressive effect of the upper airway feedback on ventilation is greater in young animals appear highly relevant to the etiology of SIDS.

Processes Basic to Reading

The NICHD currently supports an unusually interesting and potentially important study in the basic reading processes in Yugoslavia. A number of different experiences are being conducted that focus on the basic information-processing steps involved in letter and word recognition. These experiments take advantage of the fact that Serbo-Croatian, the language of Yugoslavia, uses two orthographies (alphabets); both the Cyrillic and the Roman alphabets are entirely phonetic and each is read with equal facility by many Yugoslavs. The research exploits this situation, making possible detailed comparisons with similar studies conducted with English speakers at U.S.-based laboratories under NICHD support. The emphasis in this research is on the units of recoding from visual to phonetic form and on the linguistic level at which visual inputs merge into the processes of speech. For example, in one experiment subjects are shown successive tachistoscopic (flash projector) presentations of letters (Roman-Roman, Roman-Cyrillic, etc., a procedure designed to create a masking effect;subjects must attempt to identify the letters. The institute anticipates significant, new information from studies of this type that will lead to a better understanding of the normal reading process and those factors that interfere with or prevent many children from acquiring this essential skill.

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U.S.-U.S.S.R. Medical Science and Public Health Cooperative Agreement

Under the public health part of the U.S.-U.S.S.R. Cooperative Health Agreement, NIEHS and several other American research institutes have developed a collaborative research program with several Soviet scientific institutes to explore three problem areas in environmental health: the methodologic basis to assess the biologic effects of inhaled chemicals; the methodologic basis to assess the biologic effects of orally introduced chemicals; and the scientific basis to assess the complex biologic effects of chemicals inhaled and introduced orally. These three problem areas are subdivided into eight specific research subjects. U.S. participation in this effort is under the overall coordination of the director, NIEHS.

1975 was the third year of formal cooperative efforts in environmental health between the United States and U.S.S.R. The first year was concerned largely with establishing working relationships and agreeing on areas of joint study. Initiation of joint research efforts began in the second year of the agreement and involved exchange visits between scientists of both sides.

In December 1974, U.S. and Soviet researchers participating in the agreement met at the invitation of the Soviet government in Riga, Latvia, to present the results of their cooperative effort to date. Five NIEHS scientists attended this meeting. The results of this symposium will be published in 1975 in both the United States and the Soviet Union. A cooperative research program for 1975-1976 was agreed upon during the Riga symposium.

By the end of 1975, over 20 scientific papers will have been published by U.S. and Soviet scientists on environmental health research conducted under the auspices of this agreement.

An initial draft of a Russian-English glossary of environmental health terms was prepared during 1974 and is currently under review by both countries. A first edition of this glossary will be published in 1975 in both countries.

U.S.-U.S.S.R. Agreement on Cooperation in the Field of Environmental Protection

NIEHS participation in this agreement, which spans the most significant aspects of problems of the environment, is focused on the area of the "biologic and genetic effects of pollutants." The director, NIEHS, serves as HEW representative to the Environmental Protection Agreement and as co-chairman of the working group for the problem area concerned with the biologic and genetic effects of pollutants. Cooperation in this area, involving scientists from NIEHS, EPA, and university laboratories, is focused on the mutagenicity of environmental contaminants, the toxic effect of heavy metals in the environment, psychophysiologic factors, and epidemiology. Program activity in 1975 consisted largely of information exchange and a joint workshop in New York City in April on "Basic and Practical Approaches to Environmental Mutagenesis and Carcinogenesis."

Investigation of Inhaled Pollutants under the U.S.-French Agreement for Scientific Cooperation

In fulfilling its responsibilities under the agreement reached between NIH and the Institut National de la Sante et de la Recherche Medicale (INSERM) in May 1970, the National Institute of Environmental Health Sciences sponsored Dr. N. LeRoy Lapp, Appalachian Laboratory for Occupational Respiratory Diseases, NIOSH, during his exchange visit to Dr. Sadoul's laboratory in Nancy, France, from September through December 1974.

NIEHS has reviewed its participation in the program and has recommended that further participation by NIEHS be discontinued with the proviso that in the future, as priorities and resources allowed, NIEHS would again like to be an active participant.

U.S.-Japan Cooperative Medical Science Program

Dr. Charles Langley, Environmental Mutagenesis Branch, NIEHS, attended the Third Joint Conference of the Panel on Methods for Evaluating Environmental Mutagenesis and Carcinogenesis in Tokyo, Japan, August 1974.

Cooperation with the World Health Organization

NIEHS has continued its cooperation with WHO in several activities. Dr. Hans L. Falk, Associate Director for Program, NIEHS, attended the first WHO conference on the "Assessment of Potential Health Hazards from Technological Developments," held in Geneva, September 1974. Dr. Falk is involved in preparing a follow-up series of international conferences, sponsored jointly by WHO and NIEHS, on health hazards resulting from established or newly developed technologies. The first of these conferences, dealing with the rubber and plastics industries, will be held at NIEHS during fiscal 1976.

A WHO program to prepare international health criteria documents on important environmental pollutants has produced over a dozen documents that have been directed to NIEHS for comment and evaluation.

Dr. Falk has been involved in the planning of a manual on the evaluation of the toxicity of chemicals, including the preparation of a chapter on modifying factors, mechanisms of potentiation, and antagonism, for completion in early 1976.

Dr. Falk represented WHO at the meeting on "Impact of Production and Use of Energy on the Environment" sponsored by the United Nations Environmental Program (UNEP) in New York, February 1975.

Dr. Robert L. Dixon, Chief, Environmental Toxicology Branch, NIEHS, met with the task group of the WHO Expanded Programme of Research, Development and Research Training in Human Reproduction in Geneva during November 1974 for the review of applications for research grants. Dr. Dixon also participated in the WHO/FDA coordination of toxicology guidelines for intracervical devices in January 1975.

Dr. Robert E. Staples, Environmental Toxicology Branch, NIEHS, attended a meeting of the WHO Teratology Task Group in London during January 1975 to discuss teratology of medicated and nonmedicated IUDs.

Drs. H. V. Malling and George Mohn, Environmental Mutagenesis Branch, NIEHS, participated as members of a working group on the "Evaluation of Carcinogenic Risk of Chemicals to Man" in Lyon, France, April 1975.

To facilitate further cooperation between NIEHS and WHO, the WHO has begun to take the necessary steps toward officially naming NIEHS a WHO cooperating center.

In cooperation with the International Agency for Research on Cancer (IARC, Lyon, France, a sister organization of WHO), Dr. Falk has been involved in the preparation of monographs on the evaluation of carcinogenic risk of chemicals to man. Dr. Falk has prepared background documents on four chemicals and their derivatives: asiaticoside, cantharidin, carrageenans, and cholesterol.

Seminars Sponsored by NIEHS

Dr. F. Oesch, Department of Pharmacology, University of Basle, Switzerland, presented a seminar entitled, "Epoxide Hydrases: Inducible Enzymes Involved in the Inactivation of Carcinogenic and Cytotoxic Metabolites Derived from Aromatic Olefinic Compounds," July 1974.

Dr. H. Uehleke, Institute of Pharmacology, University of Tubingen, West Germany, presented a seminar entitled, "The Metabolism of Haloalkanes and Their Covalent Binding to Tissue Macromolecules," August 1974.

Dr. B. Ketterer, Middlesex Hospital Medical School, London, England, presented a seminar entitled, "Studies of Ligandin and Glutathione-S-Aryl Transferase Activity in Rat Liver Cytosol," September 1974.

Professor P. Armitage (London School of Hygiene and Tropical Medicine), Dr. P. Lee (Tobacco Research Council Labs, England), and Dr. R. Peto (Oxford University, England) made presentations at the NIEHS Wrightsville Beach Conference on "Extrapolation of Risks to Man from Environmental Toxicants on the Basis of Animal Experiments," held at Wrightsville Beach, North Carolina, September 1974.

Dr. M. Ahmad, Institute of Biology, Islamabad, Pakistan, presented a seminar entitled, "A Trystophanyl tRNA Synthetase Mutant in Neurospora crassa," October 1974.

Professor C. Rappe, Department of Chemistry, University of Umea, Sweden, presented a seminar entitled, "Environmental Chemistry of Some Chlorinated Hydrocarbons, November 1974.

Dr. G. M. Holder, University of Sydney, Australia, presented a seminar entitled, "In Vitro Metabolic Studies of Benzo(a) pyrene in Rat and Mouse by Liquid Chromatography," November 1974.

Dr. B. Charlesworth, University of Sussex, England, presented a seminar and discussed research programs, February 1975.

Dr. D. V. Parke, Department of Biochemistry, University of Surrey, Guildford, England, presented a seminar entitled, "Recent Developments on Biphenyl Hydroxylation as a Model Enzyme System for Monitoring Carcinogens," March 1975.

Dr. T. Matsushima, National Cancer Center Research Institute, Tokyo, Japan, presented a seminar entitled, "Effects of Microbial Protease Inhibitors on Carcinogenesis and Metastasis," March 1975.

Dr. E. Evans, Sir William Dunn School of Pathology, Oxford, England, presented a seminar on "The Cytogenetics of Inversions in Mice," March 1975.

Eight foreign scientists participated in the workshop to discuss international coordination of research in environmental mutagenesis, May 1975: Dr. C. Ramel, University of Stockholm, Sweden; Dr. P. Oftedal, University of Oslo, Norway; Dr. Y. Tazima, National Institute of Genetics, Sizouka-Ken, Japan; Dr. B. Bridges, University of Sussex, Brighton, England; Dr. N. Loprieno, Institute of Genetics, Pisa, Italy; Dr. U. Ehling, Institute for Biology, Munich, West Germany; Dr. K. Sundaram, Bhabha Atomic Research Center, Bombay, India; Dr. H. Boehme, Inst. Fuer Kultur-Pflazenforschung, Gatersleben, East Germany.

Dr. R. Fahrig, Central Laboratory for Mutagenesis, Freiburg, West Germany, presented a seminar entitled, "A Mammalian Mutagenicity Spot Test: Induction of Genetic Alterations in Pigment Cells of Mouse Embryos with X-Rays and Chemical Mutagens," May 1975.

Dr. W. Muller, Bielefeld University, West Germany, presented a seminar entitled, "Base and Sequence Specificity of DNA-Complexing Agents," June 1975.

International Visits of NIEHS Staff

July 1974

Dr. J. McKinney presented a paper at the Third International Congress of Pesticide Chemistry in Helsinki, Finland. Dr. McKinney also visited the laboratories of Dr. G. T. Brooks, University of Sussex, England, to discuss mutual research interests.

Drs. F. Andrew and R. Staples attended the annual meeting of the Teratology Society in Vancouver, Canada.

Dr. F. de Serres met with Dr. Stitch in Vancouver, Canada, to discuss marine research.

August 1974

Seven scientists from the NIEHS Pharmacology Branch presented papers at the Pharmacology Society Fall Meeting in Montreal, Canada.

Dr. D. Hoel attended the Eighth International Biometric Conference in Constanta, Romania.

Drs. R. Maurer, J. McLachlan, and R. Staples attended a meeting of the Society for the Study of Reproduction in Ottawa, Canada.

NIEHS sponsored a trip by Drs. Roy Albert and Bernard Goldstein to Moscow, U.S.S.R., to participate in the U.S.-U.S.S.R. Environmental Health Agreement.

September 1974

Dr. W. Sheridan traveled to Stockholm, Sweden, and Munich, West Germany, for discussions with mutagenic researchers.

Dr. L. Valcovic traveled to Munich and Uppsala, West Germany, to discuss current research programs and to present seminars.

October 1974

Drs. F. de Serres, W. Jurgelsky, and M. Lieberman attended the XI International Cancer Congress in Florence, Italy.

Dr. E. Soares traveled to Toronto, Canada, for continuation of collaborative research efforts with Dr. Bruce.

Drs. Rall, Dixon, Gardner, Schambra, Staples, Drew, and Ms. Lange traveled to Moscow, U.S.S.R., to participate in the U.S.-U.S.S.R. Environmental Health Agreement.

April 1975

Dr. H. Malling visited the Department of Genetics, University of Edinburgh, Scotland, and the Radiation and Environmental Hazard Research Laboratory, Munich, West Germany.

Dr. H. Falk met with a group of experts concerned with marine pollution in London, England.

May 1975

Drs. J. Fouts and J. Bend visited with Dr. Stitch in Vancouver, Canada, to discuss mutual research concerns.

Drs. G. Hook and J. Crapo attended an international conference on lung diseases in Montreal, Canada.

Dr. F. de Serres participated in the International Symposium on Genetic Hazards to Man from Environmental Agents in Ottawa, Canada.

Dr. C. Langley presented a paper at the Symposium on Human Population Monitoring methods for Detecting Increased Mutation Rates in Freiburg, West Germany, and visited laboratories in England and Denmark.

Dr. J. Woods attended the First International Porphyrins Meeting in Freiburg, West Germany.

Dr. D. McRee attended the International Microwave Power Symposium and the American National Standards Institute meeting in Waterloo, Canada.

Drs. Lucier, McLachlan, and Schambra traveled to Moscow, U.S.S.R. to participate in the U.S.-U.S.S.R. Environmental Health Agreement

June 1975

Drs. D. Rall, F. de Serres, G. Lucier, and J. McLachlan attended the joint meeting of the European Society of Toxicology and the U.S. Society of Toxicology in Montpellier, France. Dr. de Serres also traveled to Brussels, Belgium, to attend a workshop on rapid screening tests to predict late toxic effects of environmental chemicals and to Paris, France, to participate in a conference "From Molecular Recognition to Perception." Drs. Lucier and McLachlan also visited research laboratories in Stockholm and Lund, Sweden.

Dr. R. Drew attended an international conference "Radioactive Anomalies and Their Biological Implications," Pocos de Calda, Minas Gerais, Brazil.

International Visitors to NIEHS

Dr. G. Rentsch, Professor of Pharmacology, University of Heidelberg, and Research Director, Toxicology Research, Sandoz Ltd., Basle, Switzerland, was a guest of Drs. Hook and Fouts. While here, he discussed research with various branch scientists, gave an informal seminar, and demonstrated a technique for animal whole body perfusion (July 1974).

Dr. Drew described aerotoxicology programs and showed the inhalation facilities to Dr. Komal, Undersecretary of State for Public Health, Thailand, and Dr. Sonchai, Director of the Thailand National Cancer Institute (August 1974).

Dr. S. S. Parmer from India and currently visiting professor, Department of Physiology and Pharmacology, University of North Dakota, visited the Pharmacology Branch as a guest of Dr. Chhabra and discussed research with various branch scientists (September 1974).

Drs. Fouts and Drew met with Dr. C. Szymezykiewicy, Director of the Institute of Medicine in Mining and Metallurgical Industries, Zabrze, Poland, and discussed branch research and mutual interests in solvent toxicity and aerosol toxicology (September 1974).

Dr. Hart hosted a visit by Dr. Justyna Wisnieska-Knypl, Lodz, Poland. Dr. Wisnieska-Knypl discussed research programs, visited several branch laboratories, and learned liver perfusion techniques while here (November 1974).

Professor Christoffer Rappe, Department of Chemistry, University of Umea, Sweden, visited Dr. J. D. McKinney at NIEHS for research discussions on chlorinated hydrocarbon chemistry (November 1974).

Dr. Drew discussed animal and human exposures and vapor detectors with Dr. Lars Moelhave, Denmark (January 1975).

Dr. Agthe of the International Agency for Research on Cancer, Lyon, France, met with Dr. Falk to discuss common interests and problems regarding the preparation of IARC monographs (January 1975).

Dr. Preussmann, Heidelberg, Germany, visited NIEHS to discuss problems in assessment of carcinogenicity of chemicals with Dr. Falk (February 1975).

Drs. U. A. Kuzminskaya and L. V. Marston of the All-Union Institute of Hygiene and Toxicology of Pesticides, Polymers and Plastics, of Kiev, U.S.S.R., discussed with Dr. Hart possible collaborative activities with Russian counterparts in pharmacokinetics; with Drs. Hart and Eling they discussed programs on PCB pharmacokinetics and lung accumulation of xenobiotics. Dr. Drew talked with them about the technology of inhalation exposures. Dr. Fouts discussed with them induction of mixed-function oxidases (MFOs) by pesticides and the best tests for induction in humans and provided them with bibliography and reprints of selected papers on human screening tests for MFO induction by pesticides (February-March 1975).

Dr. Hart described branch research programs for Dr. R. Preussmann, Institute for Experimental Tumor Production and Tumor Treatment, Heidelberg, West Germany (February 1975).

Dr. D. V. Parke, Department of Biochemistry, University of Surrey, Guildford, England, discussed with Dr. Fouts, U.S.-U.K. cooperative programs in environmental health sciences (March 1975).

Dr. Drew discussed aerotoxicology facilities and studies with Dr. E. Poulsen, Director, Institute of Toxicology, Denmark (March 1975).

Dr. Bernard Matter, Biological and Medical Research Division, Sandoz Ltd., Basle, Switzerland, met with members of the Microbial and Plant Genetics Section to discuss the micronuclei test systems for detecting mutagenicity of environmental agents (May 1975).

NATIONAL LIBRARY OF MEDICINE

The National Library of Medicine (NLM) continued its international relationships which are based primarily on cooperative and sharing arrangements. The international character of the biomedical literature is illustrated by the fact that appoximately 64% of the 20,000 biomedical periodicals acquired by NLM annually are non-U.S. From this massive amount of material, NLM has selected with the aid of consultants, 2,300 biomedical journals which form the corpus of our computerized activity, MEDLARS/MEDLINE, and our published Index Medicus.

The Library has received many non-U.S. requests for the MEDLARS data base or for the services originating from it. Such requests were received even before the system became operational in 1964, and often from a number of institutions in the same country, all wishing to be designated as a MEDLARS center.

A primary and continuing NLM decision throughout the years has been that any international arrangements relating to the MEDLARS system should be based on substantive technical cooperation. Today, the Library has eight bilateral arrangements with Australia, Canada, France, Germany, Japan, Sweden, the United Kingdom, and the World Health Organization. Table I shows their period of operation. These arrangements represent a sharing of time, talent, and resources with no transfer of funds. In return for access to the MEDLARS system, the participating country agrees to provide: MEDLARS services to its biomedical community; a document support service; indexed input to the NLM's MEDLARS system; and to pay for personnel sent to NLM for training in indexing and searching.

The administrative setting for these MEDLARS centers varies from country to country. The National Library of Medicine has maintained a policy of requiring the participating country to select the institution from among the many who have requested being a MEDLARS center. Thus, the MEDLARS center may be in an organization which is primarily concerned with medicine or health; a library; or an organization devoted broadly to science and technology. In each case, however, the center has been given a national mandate to serve the country. (Table II)

It was envisaged that a unique role could be performed by the World Health Organization in providing service,

Table 1

NON US–MEDLARS CENTERS

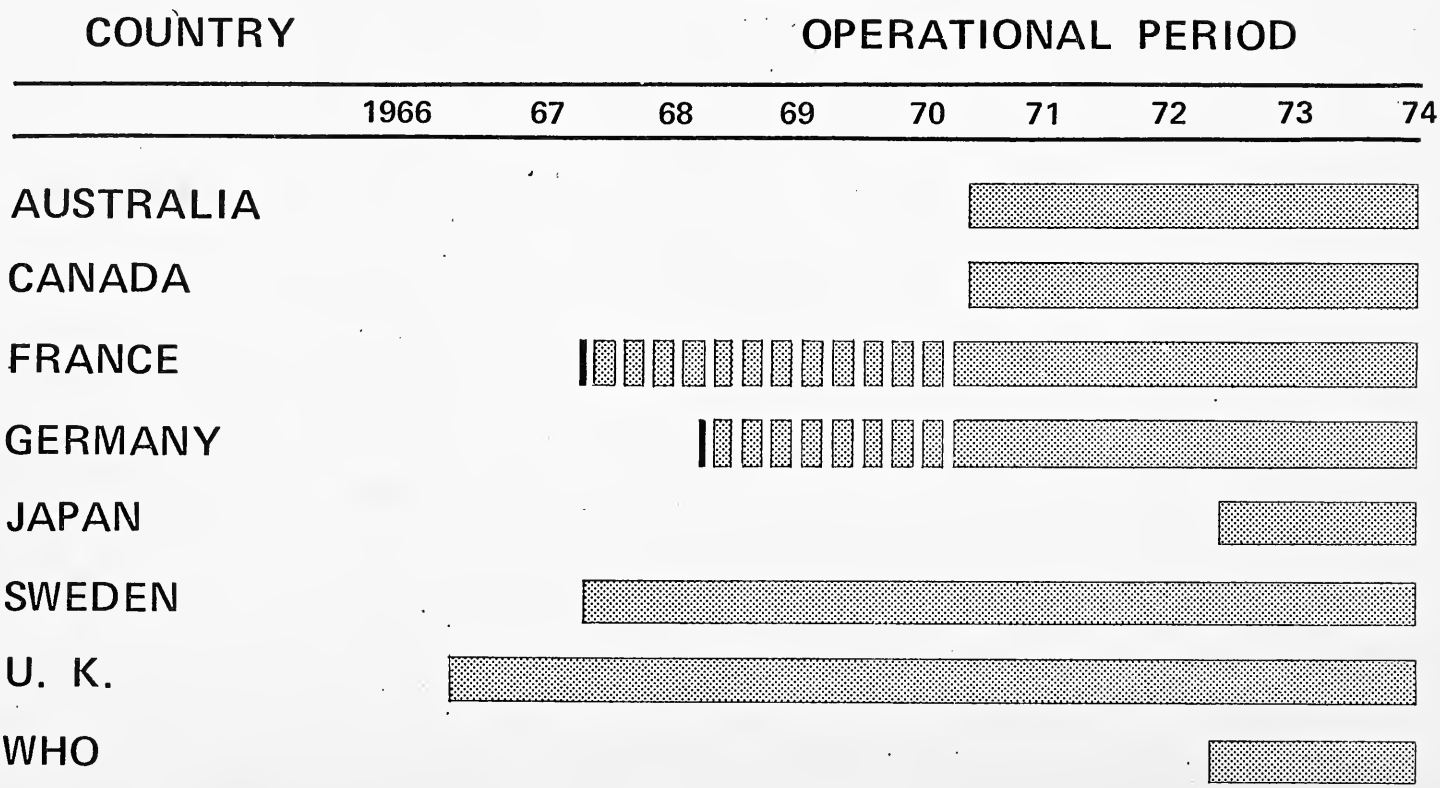

Table II

Non-U.S. MEDLARS Centers

Country	Operating Organization	Parent/Funding Organization
Australia	The National Library of Australia (NLA)	
Canada	National Science Library (NSL)*	National Research Council of Canada
France	Institut National de la Sante et de la Recherche Medicale (INSERM)	Ministere de la Sante Publique et de la Securite Sociale
Japan	Japan Information Center of Science and Technology (JICST)	Science and Technology Agency
Sweden	Karolinska Institutet	The Swedish Medical Research Council
United Kingdom	The British Library	
West Germany	Deutsches Institut fur medizinische Dokumentation und Information (DIMDI)	Der Bundesminister fur Jugend, Familie und Gesundheit
Intergovernmental Health Organization	World Health Organization (WHO)	

*Renamed Canada Institute for Scientific and Technical Information, October, 1974.

not only to its Technical Staff and Commissions, but to the developing countries that would receive information not available under other mechanisms of national auspices. WHO is in the early phases of this activity.

The current NLM bilateral arrangements reflect MEDLARS II developments. A meeting of the International MEDLARS Policy Advisory Committee was held in November 1975. This was the third such meeting of Policy Officials, accompanied by the Directors of the MEDLARS Centers. It reexamined the cooperative efforts, operational experience, regional coverage, networking, the availability of TOXLINE/CHEMLINE and future collaboration.

Exchange Programs

Through the years the Library has developed cooperative exchanges and these now number 895 exchange partners in 85 countries throughout the world. This is a mechanism for acquiring material which may not be otherwise readily obtained. The program has been under review this year to ensure that there is an equivalence to the material being exchanged.

The People's Republic of China is now an integral part of this exchange program and the Library receives five Chinese medical journals. This is in contrast to the 91 Chinese journals, including 30 major medical periodicals, which had been published and received prior to 1966.

Aid Services

The Library continues to provide services to developing countries under a special arrangement with the U.S. Agency for International Development. About 20,000 such services are provided each year to 48 developing countries throughout the world. The geographic distribution is estimated to be 29 percent to Latin America, 60.8 percent to the Near East, 8.3 percent to the Far East and 1.9 percent to Africa. This assistance responds to a demonstrated need in countries where there are insufficient medical literature resources. The services include interlibrary loans, reference requests, MEDLINE searches, loan of audiovisual materials, and subscriptions to Index Medicus and Abridged Index Medicus. Many aspects of medical research, education, public health and preventive medicine are encompassed in these services. The level of activity made possible by this NLM/AID agreement, however, does not respond totally to all needs of the developing nations.

Public Law 480 Programs

About $10,000,000 equivalent in foreign currencies of seven countries has been obligated to date for the over-all program. At present, NLM sponsors projects in Poland, Israel, Yugoslavia, Tunisia, Egypt, India and Pakistan, including analytic critical reviews and biomedical monographs, histories of medicine, secondary literature tools in the health sciences (such as guides, atlases, handbooks), translations of current and historical foreign biomedical monographs and proceedings of international conferences. There is collaboration with major U.S. scientific societies, both to determine the need for studies in special biomedical areas, as well as to arrange for distribution in the United States. University presses and professional societies, as well as the National Technical Information Service, are utilized in the dissemination of studies funded under the Library's PL 480 program.

During Fiscal Year 1975 the Library's Special Foreign Currency Program numbered 110 active projects in the seven participating countries, of which 10 were new projects. These were a monograph on the "Organization of Health Care" in Poland, a review of "Tuberculosis of the Spine" in India, a translation of a Russian monograph on "Brain and Activation," five critical reviews, and publication of two conference proceedings on enivronmental physiology and on diabetes and metabolite endocrinology. (Table III) About 70 percent of the program (primarily critical reviews) is prepared in Poland and Israel, with the remainder (largely translations) carried out in Tunisia, Egypt, India and Pakistan. During FY 1975 sixteen publications resulting from PL 480 support were received.

Foreign Visitors

The Library receives more than 1,000 visitors annually from other countries - physicians, medical librarians and information specialists. In furthering the exchange of information and ideas, the Library arranges special programs for these visitors consistent with their professional responsibilities. Of concern to the many visitors to the Library were topics such as the concept of a national biomedical information resource; specialized information activities in cancer, cardiovascular diseases and toxicology; health care and computer aided instruction. There were numerous study teams which included groups from Japan, Sweden, Pakistan, Germany, Algeria, U.S.S.R., Iran, Mexico, Trinidad and Tobago, and Egypt.

In January 1975 Dr. O.K. Harlem was appointed as a Visiting Scientist at the National Library of Medicine for one year. Dr. Harlem is a specialist in pediatrics, has been a general practitioner, a hospital physician, a university teacher and an editor. Dr. Harlem's contributions are in both the substance of medicine and in the communications and publication of biomedical information. He is developing a monograph during his stay at the National Library of Medicine which will form the basis of a course in biomedical communications within a medical school curriculum.

National Biomedical Information Centers

The National Library of Medicine, functioning as a national biomedical information resource, has attracted the interest of a number of governments who have expressed interest in establishing national biomedical information centers. The NLM does try to assist on a technical consultation basis. Although it does not provide foreign fellowships or have a formal training program, it is responsive to requests for the specialized training of physicians and information specialists who have been designated to direct a national information activity in their own country.

Two specific arrangements have developed with Egypt and Iran. In October 1974 the Assistant Secretary for Health, HEW, and the Minister of Health of Egypt held a U.S.-Egyptian Joint Working Group meeting on Medical Cooperation. As a direct result of this meeting, the Chairman of the Board of Regents of NLM and the Library's Assistant Director for International Programs met with Egyptian officials to discuss potential collaboration in biomedical information. In July 1975 the second meeting of the full Joint Working Group met in Washington, D.C., at which time the Assistant Secretary, HEW, and the Minister of Health of Egypt agreed that both parties recognize that biomedical information is a necessary component of biomedical research, education and the delivery of health services. It was also agreed to explore cooperative arrangements which will result in improved biomedical communications between and within both countries. In particular, experiences will be shared which relate to the development of a national biomedical information resource and an operational national medical library system.

At the request of the Minister of Science and Higher Education of Iran, the NLM has assisted in the planning of a national medical library and also in determining what bilateral cooperative relationships could be developed between the Imperial Medical Center of Iran and the U.S. National Library of Medicine. As a result, Iran is in the early stages of developing a national medical library and

information resource. On May 12, 1975 the Director of the National Library of Medicine and the Minister of Science and Higher Education of Iran signed a Memorandum of Understanding under which NLM will provide technical consultation, training and specialized services as requested and funded by Iran.

Regional Programs for Biomedical Information

The regional approach taken by the Pan American Health Organization (PAHO) in its establishment of a Regional Library of Medicine (BIREME) in Sao Paulo, Brazil in 1967 has resulted in an effective operational activity. The NLM serves as a technical consultant and backstop to PAHO and BIREME.

Since its first full year of operation in 1969, the collection of the Regional Library has been strengthened and the staff has increased both in number and in professional expertise. BIREME has performed 218,000 loan services; prepared 5,255 special bibliographies; obtained and donated 266,000 journal issues to other Latin libraries and has provided specialized training to 263 Latin health science librarians.

As a result of the meeting of the Latin American Ministers in 1972, PAHO and BIREME have entered into agreements with Argentina, Peru, Chile, Colombia, Uruguay and Venezuela. Each of these countries is in the process of establishing a national center so that the transmittal of services can be channeled between BIREME and that focus. However, considerable effort is still needed to strengthen these national entities and crystallize their relationships into effective service linkages.

The success of this PAHO undertaking has demonstrated that, even with political constraints and economic considerations, it is possible to cross boundaries with a regional/international effort devoted to the substance of biomedicine and the provision of information services. It is a recognition that improved biomedical communications will assist in the advancement of medical research, education and ultimately health care.

The World Health Organization has been interested in developing such regional approaches in other areas of the world. To date, no formal step has yet been taken.

International Organizations

The National Library of Medicine has continued its membership in the International Council of Scientific Unions Abstracting Board (ICSU AB) and participates in

the deliberations of this organization. The organization is a meeting ground for information and abstracting organizations, private and governmental, from a number of countries throughout the world, including the United Kingdom, France, Germany, Poland, Japan, South Africa, Canada, Belgium, The Netherlands and USSR. Important topics under consideration by ICSU AB are standardization, the economics of primary and secondary publications, the relationships between primary and secondary services and the information needs of developing countries. The 1976 meeting of ICSU AB will be hosted by the National Library of Medicine in Bethesda.

NIH ASSISTANCE TO WHO AND PAHO

During FY 1975 NIH continued to participate in activities of the international organizations, particularly the World Health Organization (WHO) and the Pan American Health Organization (PAHO).

At the request of the Office of International Health (OIH), NIH program areas assisted in the review of technical documents, working papers, and other program materials, and participated in the formulation of U.S. positions, many in connection with meetings of the governing bodies of the World Health Organization (World Health Assembly), the Pan American Health Organization (Pan American Sanitary Conference), and the International Agency for Research on Cancer (Governing Council).

NCI and FIC continued to participate with the OIH and the Department of State in defining the roles of international cancer agencies, including WHO, IARC, and the International Union against Cancer, and in defining WHO's role in the development and coordination of biomedical research. The NIH Director continued as a member of the PAHO Advisory Committee on Medical Research.

NIH officials participated in formal meetings of international organizations, including service on U.S. delegations to meetings of their governing bodies. The Deputy Director, NCI, served as the U.S. representative to the 2-day annual meeting of the Governing Council of the International Agency for Research on Cancer (14th session, May 1975) and represented the United States at the WHO meeting of heads of medical research councils (December 1974).

The National Library of Medicine continued to collaborate with activities of the PAHO Regional Library of Medicine, established at the Federal University of Sao Paulo, Brazil, which provides services in the health sciences to all of South America. The NLM Director participated in the Seventh Meeting of the Scientific Advisory Committee.

The Director, Center for Population Research, NICHD, continued to serve on the Advisory Group to the WHO Expanded Program of Research, Development, and Research Training in Human Reproduction. This WHO program focuses on the urgent need to develop a variety of safe, effective and acceptable methods for the regulation of human fertility.

During FY 1975, six NIH laboratories continued to serve as Regional or International Collaborating Centers

for the World Health Organization: Collaborating Center for Immunology, NCI; Collaborating Center for Malaria, NIAID; Collaborating Center for Respiratory Viruses Other Than Influenza, NIAID; Collaborating Center for Human Rickettsioses, NIAID; Collaborating Center for Comparative Medicine, NCI; and Collaborating Center for Mycoplasmas, NIAID. In May 1974 the Division of Research Services, NIH, was designated as the WHO Collaborating Center for Defined Laboratory Animals.

Several NIH programs contracted to support specific activities of PAHO, WHO, and IARC. NIAID, for example, supported the First Inter-American Conference on Conservation and Utilization of American Nonhuman Primates in Biomedical Research, held in Lima, Peru, June 2-4, 1975.

Some 50 NIH scientists served as advisors or consultants to WHO/PAHO. Two NIH employees were on long-term detail to WHO and one each to PAHO and IARC. An NLM official, transferred to WHO, continued to serve as chief of WHO's Library services. During the fiscal year many NIH staff members continued to serve as members of a variety of WHO expert advisory panels and participated in their committee meetings.

Two programs (NIEHS and NIAID) were provided consultant services by WHO. (This WHO activity provides "technical assistance" to U.S. domestic programs.)

UNITED STATES FELLOWS AND TRAINEES ABROAD

The sponsoring of U.S. Fellows and Trainees for Research and Training Abroad began with the establishment of the several insitutes at NIH. The criteria originally developed to select training locations for fellows and trainees provided that they might attend any qualified institution in the United States; study abroad was authorized only when satisfactory evidence was provided that the type or quality of training abroad was particularly suited for their purpose and could best be obtained there. This program, which is administered by the individual institutes, began with one fellowship award made in 1947. The peak year for U.S. fellows and trainees abroad was FY 1966 with 397 awards. Since FY 1966 foreign training has been reduced due to budgetary controls.

GUEST WORKERS

Under the Guest Worker Program, the NIH may invite individuals, other than employees or fellows of the NIH, who are sponsored by qualified organizations to utilize the research facilities of the NIH for the purpose of carrying on a research project or participating in a research program. The basis for acceptance of a guest worker rests on complementary professional interest, appropriate facilities, and the prospect of mutual benefit to the host bureau, institute or division and the guest worker. During FY 1975, 184 scientists from 42 countries worked at the NIH under this program.

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U.S. DEPARTMENT of HEALTH, EDUCATION, and WELFARE

Public Health Service